AGING In Today's Environment

Committee on Chemical Toxicity and Aging
Board on Environmental Studies and Toxicology
Commission on Life Sciences
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Preface

In 1985, the Environmental Protection Agency (EPA) and the National Institute of Environmental Health Sciences (NIEHS) asked the National Academy of Sciences to evaluate current information about the effects of environmental chemicals on aging processes and the aged population and to recommend research strategies in this area. In response to this request, the National Research Council's Board on Environmental Studies and Toxicology established the Committee on Chemical Toxicity and Aging. The formation of the committee constituted one of the country's first organized efforts to bring together experts in the fields of gerontology and toxicology to consider the interface between the two scientific disciplines.

For many topics, the government has seen fit over the years to organize interagency groups to ensure information exchange and coordination or to speed the implementation of specific steps to a goal. Examples include the Nutrition Coordinating Committee, the Biotechnology Coordinating Committee, and groups concerned with such topics as radiation and regulatory matters. These groups have a mixed record of effectiveness. Often they are created by one administration but then fall into disuse and disappear with the next. Still, for those subject areas that are of interest and concern to many different agencies and that can

benefit from a forum for discussion and coordination, the idea of forming such a committee is attractive.

Aging is such an area. The responsibility for research and policy formation for aging is found in several agencies: The major focus of basic research and training is at the National Institute on Aging (which includes the Interagency Committee on Aging Research), a major clinical training function is carried out by the Veterans' Administration, and there are several policy coordinating groups at the level of the Assistant Secretary for Health at the Department of Health and Human Services. Although it was beyond the scope of this committee's task to evaluate government programs on aging, the need was apparent to this committee for an increased effort in coordinating and conducting research on aging that would include toxicology.

This report, which is the result of the committee's deliberations, reviews the important environmental factors that influence the aging processes and the aged, and it recommends research that needs to be done to improve our understanding of aging in today's environment and the health and well-being of the aged population.

On behalf of the committee, we would like to express our appreciation to the National Research Council staff and others who facilitated this committee's deliberations and work in preparing this document. We specifically thank Andrew Pope for his skillful writing, editing, and facilitation of committee process, Jeanne Richards for her enthusiastic contributions in literature research and drafting of materials, Edna Paulson for her tireless dedication to accuracy in reference verification, Devra Davis for her valuable guidance and creative oversight, Alvin Lazen for his sound direction and sage advice, and Norman Grossblatt for his professional judgment and logic in editing the report.

We are also grateful to the sponsors, EPA and NIEHS, and to the project officers from those agencies: Scott Baker for his visionary planning, initiation, and continued support of this project, and Linda Birnbaum for her enthusiastic technical guidance and assistance.

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Executive Summary

This report examines the relationships between aging and exposure to environmental agents (including natural and man-made agents, as well as life-style factors). Several relationships must be considered—the impact of intermittent or lifelong exposure to environmental agents on the rate of aging, the impact of lifelong exposure on health status when one reaches more advanced age, and the special response of the aged compared with that of the young when exposed to environmental agents.

There are clear indications that these impacts exist. Exposure to sunlight ages the skin. Animal studies indicate that diet influences longevity. It is known that older people may respond differently to environmental and life-style factors than do younger persons. Ambient air that is well tolerated by an exercising young adult may compromise the health of an 85-year-old with impaired respiratory function.

Unfortunately, too little is known to permit definitive conclusions to be reached about the relationships at this time. Yet, given the importance of the problem, this committee felt that it is essential to gather in one document the pertinent data that do exist, to examine them for clues and directions for future research, to seek some theoretical and practical frameworks for addressing the issue, and to suggest a course of research.

From the age of 30, many of our physiologic systems begin to decline, and by old age, our overall homeostatic reserve—our ability to respond adequately to environmental stress or toxic insult—has also declined. The extent to which the environment influences the patterns of disease and functional impairment in aged populations may not now be known. But the amount of the decline caused by lifetime exposure to harmful environmental agents and the amount caused by basic, underlying aging processes are questions of great theoretical and practical significance, given the demographic patterns that show an increasing percentage of older persons in the population.

Although the increased incidence of chronic diseases is often associated with aging, such diseases need not be characteristic of the aging processes. The wide variation in the incidences of chronic diseases in the aged in different countries strongly indicates that much of the prevalence of these diseases might be preventable. Thus, old age can occur in the absence of disease. One appealing and testable hypothesis is that reduction of disease in old age can be approached, in part, through modification of the environment. Research in this field will likely lead to an improved understanding of the relationships that exist among aging processes, the environment, and disease and assist in providing the key to preventing environmentally induced age-associated diseases.

The study of the relationships between aging and the environment requires the integration of the two disciplines of gerontology and toxicology. Gerontology is the scientific study of aging, under which several theories of aging have been developed. Although none of these has been universally accepted as a satisfactory explanation of all the phenomena of aging, taken as a whole the theories begin to account for some of the underlying processes. In general, current theories of aging invoke either alterations in genetic factors or alterations in body function as the underlying causes of age-associated decline. The dilemma created by the lack of a unified theory of aging is that the intrinsic aging processes have not been clearly separated from natural disease or toxic response and thus cannot be defined.

A primary objective of the science of toxicology is to determine the potential health effects of exposure to chemical and physical agents, often through the use of animals in experimental studies. More specifically with regard to aging, toxicology can be used to study the effects of environmental agents on the aging processes

and the potential for increased toxicity of such agents in aged persons.

AGING AND NUTRITION

Until fairly recently, the issue of chemical toxicity and the environment focused primarily on contamination of the natural environment with industrial and other pollutants. As a whole, however, it appears that one of the most important chemical exposures for humans, both in quantity and in diversity, results from diet. Thus, nutrition is one of the most important aspects of the environment that should be taken into account in studies of chemical toxicity and aging.

Diet modulates many adverse effects normally associated with aging, and some dietary regimens actually promote such effects. For instance, a few studies with rodents on a restricted food intake but with ample intake of essential nutrients and other substances for which there is some evidence of antiaging action showed increased longevity. Despite claims that such a regimen will extend human life span, there is no evidence that such diets influence the aging processes of humans or that their long-term use will not, in fact, adversely affect the health of humans.

A substantial data base exists on nutritional needs of the aged, as well as on the role of nutrition in cancer and other diseases. Strategies for the determination of the mechanism by which nutrition modifies aging and chronic diseases are needed.

With regard to nutritional requirements, there is an obvious lack of data on older age groups. The commonly used reference in the United States is the *Recommended Dietary Allowances* (RDAs) published periodically by the Committee on Dietary Allowances of the National Research Council's Food and Nutrition Board. The nutrient needs of adults, however, are based mainly on studies of young adults, and many of the allowances for older adults are estimated largely by extrapolation. Although the RDAs consider seven age ranges from birth to 22 years, there are only two age ranges for people over 22—specifically, 23–50 years and 50 and older. It is appropriate to consider that the dietary requirements for people 50–60 years old may be different from dietary requirements for those over 80. In addition, the RDAs make no provision for chronic ailments that can influence nutritional needs, especially for the aged.

AGING AND SUSCEPTIBILITY TO DISEASE

Age appears to be the most important determinant of incidence for most human diseases. Characteristic patterns of risk by age have been described for most diseases, and many of the patterns have provided the basis for important etiologic theories. For example, the peak in incidence of Hodgkin's disease in the third decade of life suggested an infectious origin for one kind of Hodgkin's disease, and the plateau in incidence of breast cancer around the ages of 45–55 suggested that the cessation of ovarian function had an effect on the development of the disease. Data on the premenopausal and postmenopausal incidence of breast cancer in different countries suggested that environmental factors play an important role in the etiology of postmenopausal breast cancer, whereas genetic, endocrinologic, and other endogenous factors strongly influence the risk of premenopausal disease.

One of the most important bodily defenses is the immune system. Environmental influences on the immune system include psychologic stress (including bereavement), nutrition, environmental temperature, housing, light, noise, and chemicals. Some environmental influences on immune function affect life span (in rodents) and therefore presumably affect susceptibility to disease or to the effects of the aging processes themselves.

The thymus plays a central role in cell-mediated immune responses and the regulation of the immune response. Because thymic involution occurs by midlife (45–50 years in humans), immune senescence is characterized by a loss of thymus-dependent functions. Inasmuch as the response to many pathogens—including viruses and fungi, as well as neoplastic cells and some environmental agents—depends on cell-mediated immunity, the susceptibility of the aged to diseases induced by these agents is increased. The striking increase in the morbidity and mortality associated with influenza in elderly people is a common clinical consequence of immune senescence.

In addition to the loss of cell-mediated immunity with age, the loss of thymic function leads to the dysregulation of immune reactions. The striking increases in the frequency of autoantibodies (antibodies that have an affinity for tissues of the subject in whom the antibodies were formed) and in the production of monoclonal immunoglobulins with age reflect this fact. These autoimmune reactions might be exacerbated when elderly people take such drugs

as procainamide, α-methyldopa, or estrogens, which themselves stimulate the production of autoantibodies. When autoantibodies react with autoantigens, they form immune complexes that can contribute to vascular injury and thereby to the increasing severity of atherosclerosis in the elderly.

AGING, DISEASE, PHARMACEUTICAL USE, AND CHEMICAL RESPONSE

Along with the age-associated increase in the incidence of chronic disease comes an increase in the use of pharmaceuticals. In the United States, people 65 and over consume approximately 25% of the prescription drugs dispensed by pharmacists, although they make up only 12% of the population. Even the elderly who live independently commonly use at least one prescription drug regularly, and patients in hospitals and chronic-care institutions typically receive numerous medications. In addition, the elderly have an apparent propensity to suffer adverse reactions to drugs, and many patients, both old and young, fail to take medications according to their physicians' and pharmacists' instructions.

Studies of age differences in pharmacodynamics (biochemical and physiologic effects of drugs and their mechanisms of action) must take into account possible age differences in pharmacokinetics (absorption, distribution, metabolism, and elimination). For example, studies generally show that the elderly are more sensitive to the depressant effects of neuroactive drugs, such as diazepam, and the analgesic effects of narcotics, such as morphine; in contrast, the in vivo sensitivity of the heart to isoproterenol and its antagonist propranolol appears to decline with age.

The qualitative and quantitative differences in the ways older people tend to respond to drugs result from at least two circumstances: multiple chronic diseases are the rule, rather than the exception, and diseases are accompanied by important and sometimes subtle physiologic changes that occur with normal aging. That is, in addition to the normal age-associated changes in the immune system that affect one's ability to ward off disease, alterations in pharmacokinetics and pharmacodynamics alter the response to drug exposures. Thus, it is reasonable to assume that the elderly would tend to respond differently to environmental factors.

The percutaneous absorption of drugs and other chemicals

also increases with age, and age-associated changes in the skin render the elderly more vulnerable to some types of environmental exposure. For example, the ability to tolerate extremes in temperature is reduced in the aged, who have decreased vascular area and vasoreactivity in the skin. This also contributes to the onset of heat stroke or hypothermia in the presence of extreme temperatures.

Geriatric patients often exhibit a reduced rate of hepatic metabolism of some drugs. However, large differences in the magnitude of this effect have been demonstrated. Moreover, age effects are marked for some drugs and negligible for others. Even in the case of drugs whose hepatic metabolism is markedly impaired with age, interindividual variations caused by other factors outweigh the age effects. Nevertheless, the possibility of greatly reduced hepatic capacity exists in many elderly patients. By slightly reducing the dosage of potent drugs with low therapeutic indexes or by watching such patients especially carefully, physicians can ensure the therapeutic efficacy of prescribed medications and detect undesirable drug-related side effects early.

AGING AND ENVIRONMENTAL FACTORS

Among the best documented examples of age-associated pathologic conditions that are related to environmental factors is photoaging—the changes in skin appearance and function that are due to habitual exposure to the sun, rather than to the passage of time alone. Photoaging, also called “premature aging” and “dermatoheliosis,” is virtually synonymous in the public mind with “true” chronologic aging and has only recently been differentiated by dermatologists. Clinically, photoaging is characterized by coarseness, wrinkling, mottling, laxity, reduced elasticity, telangiectasia (dilation of blood vessels), atrophy, fibrotic depigmentation (pseudoscars), and ultimately malignant neoplasia on the face, neck, hands, and other habitually exposed body areas.

Photoaging and chronologic aging in the skin have striking similarities, but the processes can be distinguished with an electron microscope. The ability to distinguish between them offers the hope that the effect of environmental factors other than exposure to the sun might also be differentiated from intrinsic aging.

Even in the absence of “control” tissue not environmentally

exposed (a major advantage in skin), it might be possible to obtain valid information on normal morphologic and physiologic aging changes. However, it will not be easily accomplished. In middle-aged or elderly people, even casual comparison of habitually exposed skin with protected areas (e.g., face or hand versus buttock or breast) immediately suggests different aging rates, with lines of demarcation corresponding to clothing styles, rather than to anatomic or physiologic compartments. Nevertheless, the major role of the environment in skin aging has only recently been accepted, and this implies that overwhelming evidence will be required to convince both scientists and the public of other adverse environmental impacts on the aging processes.

The nervous system presents another example of how toxic agents can sometimes mimic the clinical and pathologic features of diseases more common in the aged. For example, the parkinsonian syndrome is observed in workers chronically exposed to manganese ore or carbon disulfide and in persons intoxicated for relatively short periods with methylphenyltetrahydropyridine (MPTP). Some types of motor neuron disorders have been associated with exposure to lead, polyneuropathy follows exposure to a number of occupational chemicals, and psychoses can be exacerbated by acute exposure to diisopropylfluorophosphate.

Because the nervous system appears to have a number of components that are vulnerable both to the aging processes and to toxic chemicals, older people with compromised neural structure and function, as well as reduced capacity for liver metabolism and renal clearance, are probably more susceptible to some neurotoxic substances than are younger adults. In addition, it is generally believed that the clinical expression of disordered neural function resulting from aging or chemical toxins becomes evident only after the considerable structured and functional redundancy of the nervous system has been overcome.

MODEL SYSTEMS FOR RESEARCH

The development of model systems in the field of aging is only beginning. Model systems will assist in the two-step process of testing environmental chemicals for their potential to affect aging processes or age-associated diseases and developing a data base for predicting human responses and assisting in regulatory decision-making.

Because we know so little about the fundamental nature of the aging processes, a prudent course in assessing the effects of environmental chemicals might be to use multiple model systems. The animals selected for study should meet several criteria, including short life span, previous use in the study of aging and toxicology, ability to develop under defined environmental conditions, knowledge of genetic characteristics and known pathologic changes that occur with age, ready availability, economic feasibility, widespread use in other biologic disciplines, and relevance to aspects of human aging.

A research strategy for testing should include in vitro, invertebrate, and mammalian models. In vitro models are economical and efficient, permit repeated assays and the sharing of common stock among different laboratories, and can be used to investigate cell-cell interactions, such as metabolic cooperation and transformation; however, they cannot completely eliminate the need for experimentation with intact animals. Invertebrates have short life spans, are relatively easy to use, and are relatively inexpensive; many have been widely used as models for the study of aging and meet the proposed criteria for models. However, aging of cold-blooded organisms might well be different from that of warm-blooded organisms. Mammals, because of their long life spans and other characteristics, generally do not fully meet the proposed criteria. Mice and rats are exceptions, however, and indeed have been widely used in aging research.

Epidemiologic observations will also provide a useful resource for assessing the impact of toxic exposures on the risk of disease and death in humans. Short-term and long-term chronic releases of toxic agents into the environment have markedly increased disease and death among those exposed, especially affecting the aged.

CONCLUSIONS

Evidence supports the concept of intrinsic aging or aging as a natural process, and many theories have provided insight into its basic mechanisms. Many components of the environment, however, cause changes that simulate and are often confused with features of intrinsic aging. For example, habitual sun exposure and cigarette smoking accelerate aging of the skin, exposure to ultraviolet radiation also promotes cataract formation, and exposure to naturally occurring or industrial and other toxicants can

contribute to age-related neurologic disease. However, no agent has ever been shown to cause the early appearance of *all* the aging processes.

Modifying the environment of the elderly holds considerable potential for improving their quality of life and their longevity. In addition, it seems reasonable to assume that aging consists of many intrinsic processes characterized by progressive declines in function that can take place in the absence of clinical disease. The extent to which major age-related diseases (e.g., cancer, arteriosclerosis, diabetes, osteoarthritis, osteoporosis, cataracts, hearing loss, amyotrophic lateral sclerosis, Parkinson's disease, and senile dementia of the Alzheimer's type) are coupled to underlying aging processes or environmental influences constitutes an important research question, in light of the surge in the size of this segment of the population.

In view of the paucity of basic information on aging processes, it is premature to embark on a systematic screening of environmental agents with an eye to identifying agents that influence these processes. Such an approach would be ill-advised and detrimental to progress in the field of "gerontotoxicology," the study of interactions between aging processes and the effects of environmental substances with toxic potential. Rather, there is a need to develop a better understanding of the basic mechanisms of aging, how they can be affected by the environment, and how aging itself affects toxicity.

Toxicologists should identify a group of archetypal toxic agents (reference compounds) that could be used to mimic age-associated diseases or biologic markers of aging. The likely impact of the demographic shift that is now under way and will continue into the twenty-first century will be to alter fundamentally the major social and economic commitments of this country. The development of interventions that enable the elderly to live out their lives independently and productively will mitigate the impact. Support of research into aging and into the effects of the environment on aging processes should therefore be given a high priority.

1

Aging and Environmental Exposure

Are environmental agents robbing us of both life span and life expectancy, or are we approaching natural maximums of both? Should we concentrate our research effort less on the study of aging processes and more on living longer in the midst of the noxious substances in our environment? Should we devote more effort to the study of environmental induction of age-associated disease? By eliminating the causes of age-associated disease that are not inherently related to the aging processes, we can probably increase the quality of life in old age. If mechanisms of development of disease depend more on basic underlying processes of aging than on factors that can be eliminated from such processes, the piecemeal study of the diseases of old age will have only limited success. Our inability to separate the aging processes from environmental influences lies at the heart of the problem.

Precisely how environmental agents affect aging processes is not known. The subject has not been adequately studied, and aging processes themselves have not been adequately described. However, it is reasonable to assume that environmental agents acting at critical periods of development can affect age-related phenomena later in life.

For example, exposure to an agent that affects or interferes

with the development of stem cells during the fetal stage, in infancy, or in early childhood might contribute to nervous system decline in later life. For instance, a depletion of precursors of the neurons of the substantia nigra might increase the probability of a comparatively early onset of Parkinson's disease. A change in the susceptibility to a great many other pathophysiologic accompaniments of aging might have, in part, such an etiology. In addition, the elderly might be particularly vulnerable to the effects of many environmental agents because of normal age-related alterations in cellular structure and function and a general decrease in the ability to maintain physiologic homeostasis, or because of alterations acquired as a result of environmental exposure.

The classic studies of Nathan Shock (1977) suggest that there are almost linear declines in the functional capacity of many (if not all) physiologic systems in many but not all humans after age 30. The rate of decline varies among organ systems, from 2.5% per decade in basal metabolic rate and nerve conduction velocity to 10% per decade in renal and respiratory capacity. It follows that the homeostatic reserve of the organism, which is proportional to the dynamic range of the integrated functions of physiologic systems, declines with age.

Clinical studies have revealed that a number of adaptive responses are diminished in old people. For example, body temperature is influenced by increases in ambient temperature to a far greater extent in the old adult than in the young adult. This phenomenon is attributable largely to the slower onset of vasodilatation and sweating that follows an increase in ambient temperature. Homeostatic responses are also blunted after an increase in blood glucose concentration, blood pressure, or heart rate.

Young adults are protected from environmental stresses by their homeostatic reserves. Their deaths more often result from injuries or diseases that exceed their homeostatic capacity. Over 95% of deaths in young adults can be associated with a pathologic state. However, in one study of deaths among people who were more than 85 years old, 26% of the subjects had “no acceptable cause of death” (Kohn, 1982). They might have died of environmental stresses that would have caused no mortal complications in young people.

Epidemiologic studies have shown that older patients admitted to hospitals are slower to return to good health: the duration of hospitalization and its associated mortality increase between the

ages of 35 and 75 years. Bed rest itself can so decondition an older person that the simple act of dressing after 2 weeks in bed can induce maximal heart rate in an 80-year-old.

BASIS OF THE SCIENTIFIC PROBLEM

The scientific problem of distinguishing states of disease and impaired function that result only from an essential underlying process—aging—from states that are caused by environmental exposures is complicated by the fact that aging and chronic environmental exposure are absolute concomitants. Even in the laboratory, environmental influences can be only minimized, not eliminated. The effects of diet and other essential components of the laboratory environment can be successfully reproduced and observed as changes in structure, function, and disease states in inbred laboratory animals.

However, the extent to which the characteristics of deterioration seen in animals that age in a controlled environment are predictive for animals of the same species that age in another environment is limited, as is extrapolation to different animals whether they age in similar or dissimilar environments. Furthermore, the specific effects of intrinsic aging—those produced solely by an essential, constitutive biologic process that would occur in an optimal and absolutely nonperturbing environment—have not been identified.

Gerontologists and toxicologists have assumed that interactions between aging and the laboratory environment constitute a process that can be accounted for in a "control" population. However, both groups have sought descriptors of structure, function, or disease that are relevant only for independent underlying processes of *either* aging or toxic stress. The two groups have termed these descriptors "biomarkers of aging" and "biomarkers of toxicity," respectively. Much effort is being expended in the search for biomarkers that best predict aging or toxic response in an organism, but to date these efforts have been only partially successful.

The failure to identify biomarkers as descriptors exclusively of aging or of toxicity might simply reflect our meager knowledge of the essential mechanisms that underlie these processes. Or it might reflect a basic interplay between aging and environment through homeostatic and compensatory mechanisms that make

unlikely the identification of universal and exclusive biomarkers of aging or of a specific toxic process. If toxic agents are administered for short periods at high concentrations or if aging occurs in an artificially pristine environment, the two processes might become more clearly separable. But the separation is extremely difficult to discern in experiments relevant to human beings, who age for extended periods in environments that contain multiple agents at various concentrations.

The difficulty of applying the results of experiments on aging in laboratory animals to human beings is also related to extrapolation—across wide dose ranges, from laboratory to real environment, and from laboratory animal to human being. Validity depends on various biologic assumptions, for example, as to the shape of the dose-response curve, the interactions among many agents, and the biologic similarity of the laboratory animal to the human being. In the case of aging in a multiagent toxic environment, such assumptions are difficult to propose in exact terms or, once proposed, to defend rigorously.

These problems complicate not only laboratory study of aging in a toxic environment, but also epidemiologic and demographic studies of the aging of human populations in various environments. The latter kinds of study are also confounded by our inability to distinguish between the contribution of intrinsic aging to the health status of the aged and the contribution of environmental factors. That inability confounds the determination of the type of old age we should expect in terms of life expectancy and disease prevalence.

STRUCTURE OF THE REPORT

This report describes current knowledge about the relationship between chemicals and aging from two perspectives: the effects of chemicals on the aging processes and the effects of aging on the body's ability to respond to environmental chemicals. It discusses some specific needs for research in aging and toxicology, suggests the need for a data base on “gerontotoxicology,” and guides the development of such a data base. In separate chapters, it defines and describes the aged population (Chapter 2), reviews basic principles of gerontology and toxicology to identify relationships between aging processes and environmental exposures (Chapters 3 and 4), identifies candidate situations for environmental effects

on aging processes (Chapter 5), examines possible situations for adverse environmental impacts on the elderly (Chapter 6), outlines how the use of model systems can expand the knowledge base in both toxicology and gerontology (Chapter 7), and presents the committee's conclusions and recommendations (Chapters 8 and 9).

2

The Aging Population and the Psychosocial Implications of Aging

DEMOGRAPHIC CONSIDERATIONS OF AN AGING POPULATION

Aging has been described in physiologic, psychologic, behavioral, and sociologic terms. A demographic approach, however, leads to defining aging in chronologic terms.

Demographically, it is important to distinguish between the aging of individuals and the aging of populations. Interest in the aging of individuals focuses on survival and longevity, which make aging a function solely of changes in death rates. In contrast, the aging of a population refers to whether a population as a whole is getting older or younger and is a function of changes in rates of mortality, migration, and birth. Population aging in this sense is measured in terms of such units as median or mean age, proportion of persons 65 years old and over, ratio of persons 65 years old and over to persons under 15, or some other summary unit of the age structure of the whole population.

These various measures of population aging might indicate different patterns or different directions of aging in a given population during a particular period. For example, the proportion of elderly persons (65 and older) and the proportion of children (under 15) could both be increasing. The aging of individuals and the

environmental circumstances that influence survival and longevity are of prominent concern in this report.

The older population is not a homogeneous group, and its characteristics tend to vary markedly with age. Therefore, it is sometimes useful to consider component age groups in analyses of the older population. One common set of groups is 55–64 years, 65– 74 years, 75–84 years, and 85 years and older (U.S. Bureau of the Census, 1984). In some reports, or for other purposes, different ages or age bands might have special significance; for example, 62 is the age of eligibility for Social Security benefits. Although a population's entire age range could be included in a review of demographic aspects, the older groups—specifically those over 55, 65, 75, and 85—are usually of more concern because the effects of aging on their health, social, and economic characteristics are more pronounced.

The aging of the U.S. population in the twentieth century is vividly described by a comparison of the age structure of the population in 1950 and 1980. In 1950, 8% of the population (12 million) were 65 or older, and in 1980, almost 12% (28 million) were 65 or older (Brody, 1985). The increased survival or aging of individuals in a population is measured principally, however, by an increase in average expectancy of life at birth, reductions in mortality rates, increases in proportions of the population that survive to various ages, or increases in average years of remaining life.

Life expectancy is the average number of years a person is expected to live (either from birth or from any given age) as calculated from current age-specific mortality rates, assuming that these rates will remain unchanged for the lifetime of the person. Life expectancy at birth is a summary indicator of progress in the reduction of mortality—specifically, premature mortality—and is most sensitive to reductions in infant and child mortality. This measure indicates an increase of 24.2 years in life expectancy at birth for the U.S. population during the first 80 years of this century—from 49.2 years in 1900–1902 to 73.6 years in 1980. From 1930 to 1980, the increase in life expectancy was more pronounced for persons under age 65 (+8.2 years) than persons 65 or over (+4.1 years), and much of the increase occurred between 1930 and 1954 (U.S. Bureau of the Census, 1984). Recent U.S. data indicate that life expectancy increased more between 1970 and 1983 than between 1950 and 1970 (Figure 2–1). These recent

increases resulted primarily from decreases in mortality among those 45–64 and 65–84 years old (Figures 2–2 and 2–3).

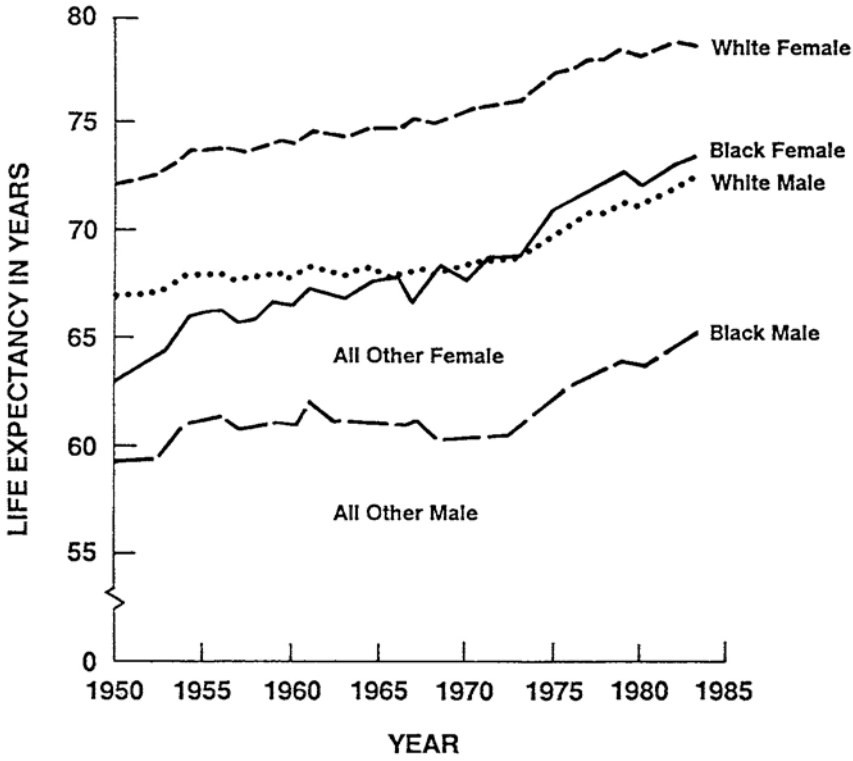

FIGURE 2–1 Life expectancy at birth by race and sex, United States, 1950–1983. Source: National Center for Health Statistics (1986a).

Life span* is the greatest age attainable by a member of a species or other group in question (Schneider and Reed, 1985). For humans, the documented life span is about 100–110 years. Gains in extending life expectancy at birth have been impressive during the past 80 years, but life span appears to have changed little, if any. Claims of unusually long-lived persons or populations, when carefully investigated, have not been substantiated (Leaf, 1982).

If the optimal life expectancy is achieved and, as suggested by Hayflick (1974), all persons live healthy and active lives until they

*Throughout this report, life span refers to maximal life span, unless otherwise specified.

reach 100 and then die peacefully in their sleep, a life-table curve of survivorship would be rectangular, rather than triangular (linear decelerating curve). The demographic life-table curves for populations from 1890 to 1978 have become increasingly rectangular, and opinions vary as to whether this pattern is likely to become more pronounced (Fries, 1980; Schneider and Brody, 1983; Siegel and Taeuber, 1986; U.S. Bureau of the Census, 1984). Figure 2–4 shows the shift in the curve for survival of white females according to current life tables for the United States.

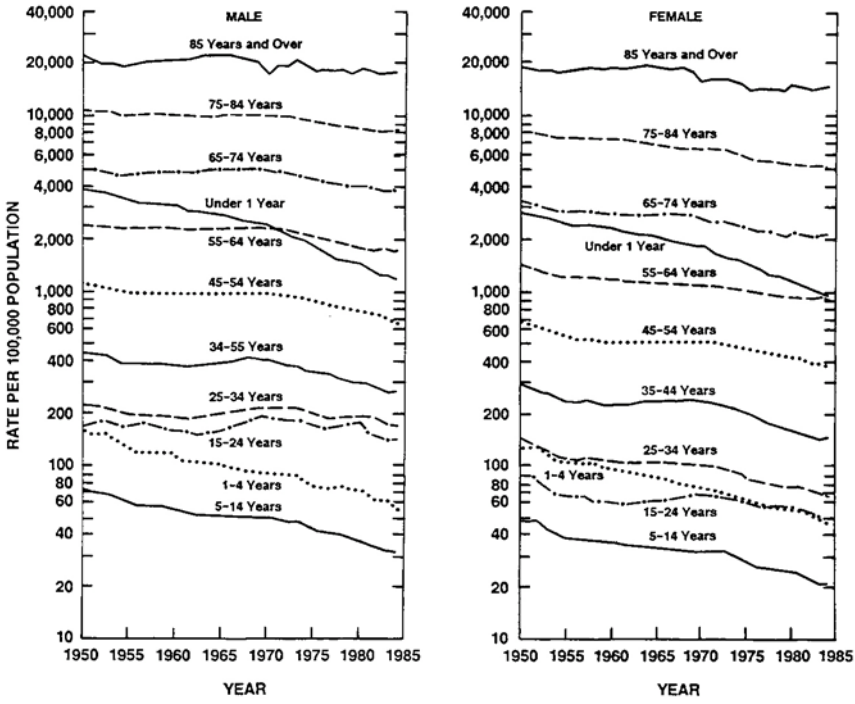

FIGURE 2–2 Death rates by age and sex, United States, 1950–1984. Source: National Center for Health Statistics (1986c).

Although life expectancy at birth has not yet reached 100 years, it has been rising almost steadily in the United States during this century. A logical extension of the present trend might be depicted by either a theoretical nearly rectangular curve (assuming a 90° angle and a steep fall just before or at the age suggested for the specified maximal life span) or a horizontal curve continuing through age 85 followed by a less steep fall (Schneider and

Brody, 1983) (Figure 2–4). It is, of course, possible that scientific discoveries could alter ideas about maximal life span. The representation of the 2050 cohort in Figure 2–4 implies the existence of a fixed maximal life span for humans. To achieve the "squaring" of the life-table curve might require several more decades, during which additional ways of extending human life might be developed and applied. The latter prediction, a flattening of the mortality curve, is reported to be more consistent with the observed mortality data for persons 50 and over (Manton, 1980), although it is controversial.

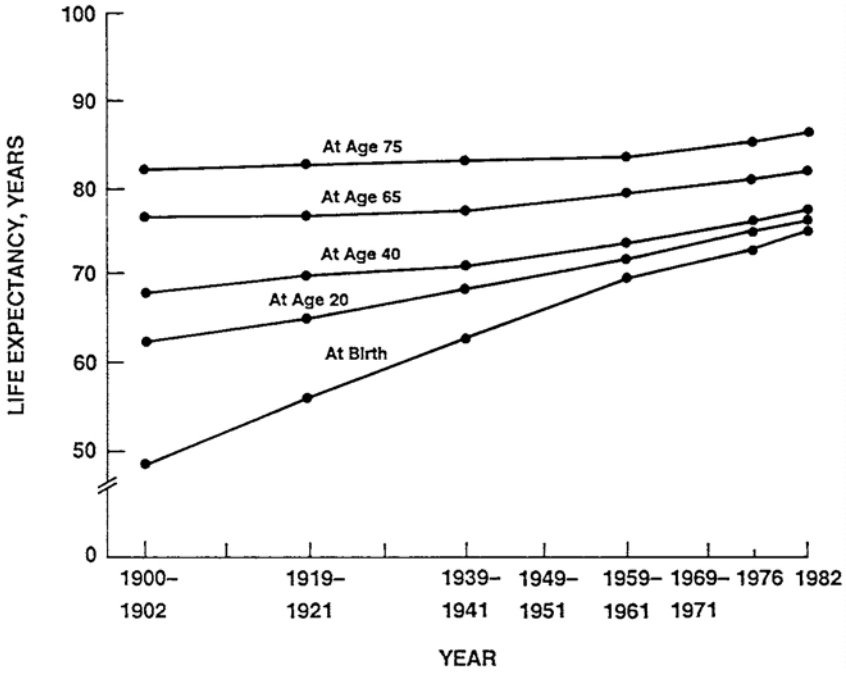

FIGURE 2–3 Average expectation of life at specified ages in selected years, 1900–1982. Source: National Center for Health Statistics (1978b, 1985b).

At the crux of the debate is the nonutility of cross-sectional mortality data, as used in a demographic life table, for examining the question of an increase in life span that results from environmental changes of the twentieth century—changes that have had a remarkable impact on mortality rates and life expectancy. True longitudinal mortality (cohort-survival) data, analogous to

survival data obtained in experimental studies, are needed to examine the question of an increase in life span in human populations (Riley, 1981a).

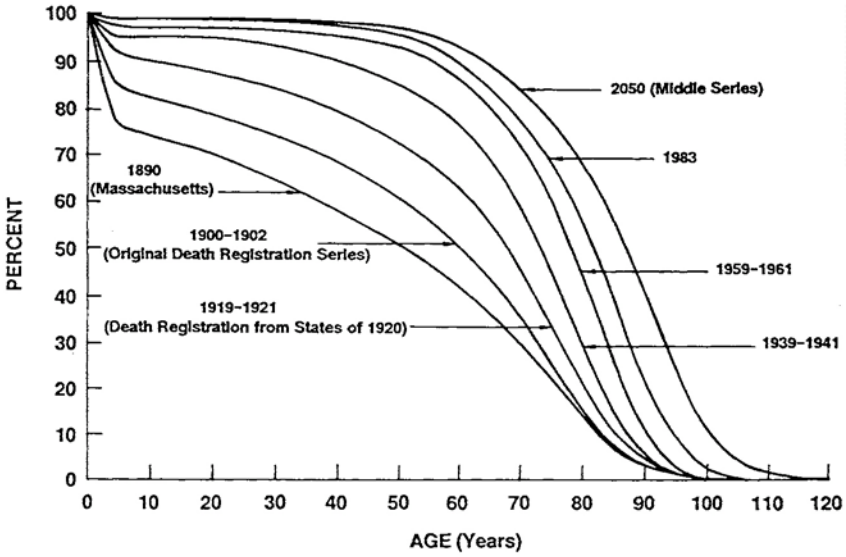

FIGURE 2–4 Percent of cohort of white females surviving to specific ages, according to current life tables for the United States, 1980–2050. Reprinted with permission from Siegel and Taeuber (1986).

The mortality of people aged 90 and over in 1980 is that of people who were born in 1890 or earlier, who were exposed to an environment vastly different from that of people born in 1980, and who are the survivors of a group that had higher mortality rates at earlier ages. A cohort life table based on the longitudinal age-specific mortality experience of cohorts born in the twentieth century is needed to assess the question of an increase in maximal life span. Although these data are not available on people over 86, among whom 15–20% of all deaths occur, the data that are available for the United States (Vandenbroucke, 1985) support the observation of a continuous increase in life expectancy at age 85 since the 1700s.

Modifications in the longevity differences within sexes and races suggest the importance of environmental (nongenetic) and genetic factors in determining longevity (Figure 2–1). Life expectancy by sex diverged progressively from 1900 to 1972. Mortality rates for males are now substantially higher than those for

females at every age, and the difference is reflected in the greater life expectation at birth for U.S. females (78 years) than males (71 years) in 1983. The lessening in the divergence since 1979 (NCHS, 1986b) suggests an environmental influence on longevity. Most of the difference is accounted for by differences in the mortality of men and women at ages over 65 and might be due in part to sex differences in smoking (Feinleib and Luoto, 1984; Miller and Gerstein, 1983; Retherford, 1972; Waldron, 1976). The divergence of death rates by sex has occurred both among whites and among blacks and people of other races, although it has been slightly greater among blacks and people of other races.

At every age and for most causes of death, females have a survival advantage. There is evidence of an intrinsic or constitutional difference in survival, but there is also evidence that the survival advantage is associated with extrinsic factors. Nevertheless, it is still unclear why females live longer than males.

Life expectation at birth for U.S. whites in 1984 (75.3 years) was substantially greater than that for blacks and people of other races combined (69.7 years). Most of this difference is attributable to the lower mortality of whites younger than 65 (Figure 2–1). In recent years, the difference in mortality between the two major U.S. racial groups (whites and blacks) has been rapidly narrowing. Most of the difference in death rates between whites and blacks at ages below 65 might result from differences in socioeconomic status between the racial groups (e.g., in occupation, education, and income) and associated differences in life-style and environmental exposures.

The death rates of blacks and people of other races exceed those of whites at all ages from 65 to 80; from age 80 on, blacks and people of other races combined seem to have lower mortality rates (Manton et al., 1979; Nam et al., 1978). The relatively favorable mortality position of blacks and people of other races above the age of 80—the "crossover effect"—suggests that socioeconomic differences are weaker determinants of mortality at ages above 65 than at ages below.

An alternative hypothesis is that the blacks who have survived the excessive environmental stresses of their earlier years might be a selected subpopulation that is genetically endowed with the ability to live an especially long life. Manton (1980) refined this hypothesis by suggesting that the crossover phenomenon might be due to the effect of genetic selection of differential mortality

rates in a heterogeneous population. According to his argument, if people in two populations are heterogeneous with respect to their endowment for longevity, crossover or convergence of the age-specific mortality rates of the two populations can occur if one population experiences markedly higher mortality at earlier ages. In our example then, those who are robust make up a larger proportion of the surviving black population than of the surviving white population as they age.

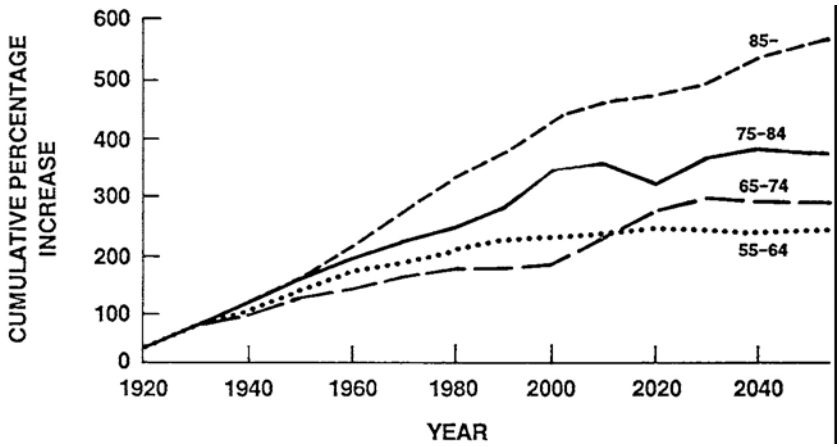

FIGURE 2–5 Percentage increase in older population, by decade, 1900–2050. Source: U.S. Senate Special Committee on Aging (1986).

The elderly population of the United States is growing much more rapidly than the population as a whole (Siegel and Taeuber, 1986). As the total population increased 11% in the 1970s, the population 65 and over increased by 28% and the population 85 and over increased by 59%. The population aged 85 and over is the fastest-increasing of the four older age groups (55–64, 65–74, 75–84, and 85 and over) and is expected to triple between 1980 and 2020 (Figure 2–5). Census projections for 2050 indicate that the proportion of the population 65 and over will be almost twice as great as today—22% compared to 12% (Siegel and Taeuber, 1986).

Fries (1980, 1983) has proposed that the period of chronic morbidity in later years will be compressed as human life expectancy approaches the theoretical maximum of 100–110 years, although the notion has been questioned (Schneider and Brody,

1983). According to Fries (1983), compression of morbidity occurs if the age at which chronic-disease symptoms first appear increases more rapidly than life expectancy. If increasing numbers of people continue to reach advanced ages (85 and over), at which rates of morbidity and concomitant physical limitations are higher, Fries's prediction does not appear likely to be realized. There is no evidence of declining morbidity and disability among the population over 65.

The *Special Supplement on Aging* in the 1985 National Health Interview Study (NCHS, 1986b) found that most people 65 and over who were living in the community were in good health on three measures—perceived health status, number of bed days, and activity limitation—although health generally declined with increasing age. One-third of people 65 and over consider themselves to be in excellent or very good health. Slightly more than 60% of those over 65 experienced no condition or illness that confined them to bed for 1 day or more.

The greatest change with increasing age was in limitation of activity; over 60% of those 65–84 reported no limitation, compared with approximately 40% of those 85 and over. However, because the subjects of the survey were not institutionalized, these data should not be interpreted to mean that the health of the total population aged 65 and over is good, especially the group aged 85 and over; healthy older people are more likely to remain in the community than those in extremely poor health.

A large proportion of the population aged 85 and over are in nursing homes (23% in 1977), and the health of people in nursing homes is generally poor. A comparison of the proportion of the U.S. civilian noninstitutionalized and nursing-home populations having activity limitation (Tables 2–1 and 2–2) shows a marked difference in the activity limitation of those 65 and over. Composite data on the total population aged 65 and over indicate that about 20% of elderly persons are disabled to some degree and a lower percentage limit their activity severely (Figure 2–6).

On the basis of comparisons with countries having the lowest overall mortality (Table 2–3), the prospects for future increases in life expectancy in the United States seem modest (U.S. Bureau of the Census, 1984), although a marked increase in the number of person-years for persons over 75 and 85 is expected. Although the decline in death rates at the higher ages is expected to slow, there is no agreement as to whether this trend will result in an increasing

rectangularization of the life-table curve (Schneider and Brody, 1983; U.S. Bureau of the Census, 1984). According to present knowledge, a life expectancy at birth of 81 years for females and 73 years for males and a life expectancy at age 65 of 21 years for females and 16 years for males appear attainable in the United States by the year 2000.

TABLE 2–1 Dependence of Civilian Noninstitutionalized Population in Activities of Daily Living, United States, 1979a

Age	Population (1,000s)	People with Activities Limited	
		1,000s	Percentage
≤18	153,177	4,852	3.2
18–44	86,378	676	0.8
45–54	22,744	526	2.3
55–64	20,713	832	4.0
65–74	14,929	1,043	7.0
75–84	6,869	1,101	16.0
≥85	1,544	674	43.7

[a]Data from National Center for Health Statistics (1983). Activities of daily living include bathing, dressing, using toilet room, mobility, continence, and eating.

TABLE 2–2 Dependence of Nursing-Home Residents in Activities of Daily Living, United States, 1977a

Age	Population	People with Activities Limited	
		Number	Percentage
All	1,303,100	1,178,700	90.4
<65	177,100	135,600	76.6
65–74	211,400	181,900	86.0
75–84	464,700	431,100	92.8
≥85	449,900	430,100	95.6

[a]Data from National Center for Health Statistics (1981a). Activities of daily living include bathing, dressing, using toilet room, mobility, continence, and eating.

These demographic trends are important because older people experience a greater share of morbidity and require a disproportionate quantity of health and social services. The large increases

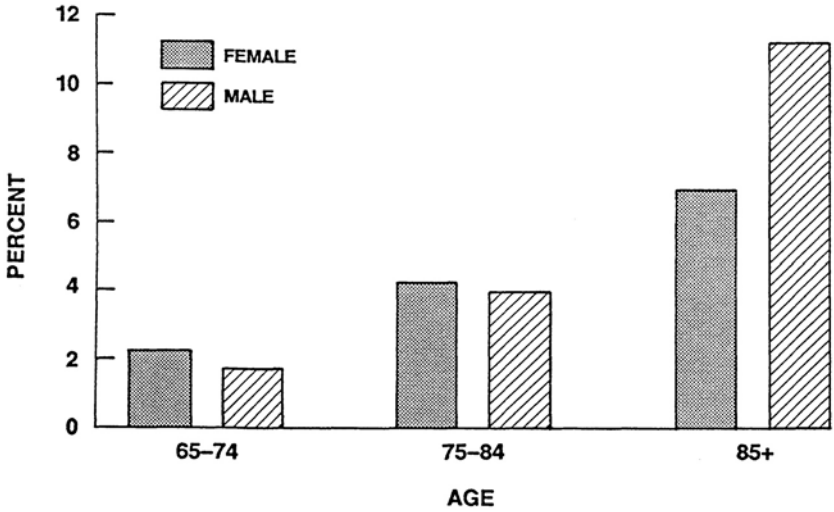

FIGURE 2–6 Percentage of population with severe activity limitation, 1982. Source: U.S. Senate Special Committee on Aging (1986).

TABLE 2–3 Life Expectancy at Birth for Females and Males in Selected Countries (1980–1984)a

Country	Life Expectancy at Birth	
	Male	Female
Japan, 1984	74.8	80.7
Norway, 1983	72.8	79.8
Australia, 1983	72.2	79.0
United States, 1982	70.9	78.4
West Germany, 1984	70.5	77.1
Venezuela, 1980	65.8	71.4
Mauritius, 1982	63.6	71.1

[a]Most recent data available at time of publication from the World Health Organization (1985); United Nations (1984).

in the numbers of people in the higher age groups in future decades will have important health, social, and economic implications.

PSYCHOSOCIAL ENVIRONMENT

Having a sense of purpose is closely tied to one's health and well-being. A Joint American Medical Association-American Nursing Association Task Force (1983) addressed improvement in the health care of the aged chronically ill and concluded that "a sense of purpose and control over one's life is integral to the health of the aged."

The elderly, especially those in institutions, are often isolated and understimulated. Many older people might also feel, justifiably, that they have lost control over their lives and environments. They are more likely to need assistance with tasks they once performed independently and to require more extensive medical care and contact with a health-care system, which often encourages obedient, "manageable" behavior (Lorber, 1975; Wills, 1978).

In addition, the psychosocial environment might actually worsen naturally declining health; interpersonal relationships are related to a variety of physical health indexes (Kiecolt-Glaser et al., 1985). Loneliness, lack of stimulation, and loss of independence can have negative effects on such factors as immunocompetence, blood cortisol and glucose concentrations, and carbohydrate metabolism. Lack of control over one's life and environment may suppress the immune system (Laudenslager et al., 1983), and this might help explain the age-associated general decline in immunocompetence. In contrast, improvement in the psychosocial environment—through an increase in activity, more social contact, and a higher degree of independence—also improves physiologic factors (Langer and Rodin, 1976; Schulz, 1980).

Studies of nursing-home residents have shown that increases in responsibility and independence affect both pyschologic and physical health. Langer and Rodin (1976) reported the effects of encouraging elderly convalescent-home residents to make a greater number of choices and to assume more responsibility for daily events. Their subjects became "more alert and active and reported feeling happier," as well as showing significantly greater health improvement than the control group. After 18 months, the mortality rate among the "responsible" (experimental) subjects fell from 25% to 15%, but rose to 30% in the control group. Schulz (1976) showed

that giving elderly people in nursing homes increased responsibility for arranging a student visitation program significantly increased their activity, satisfaction, and health. Langer et al. (1979) also found that increased control over daily events led to improvements in memory, satisfaction, and physical health among elderly subjects.

All these factors—social isolation, understimulation, and lack of control over daily events—can be chronic physiologic stressors (Arnetz, 1984; Rodin, 1986). Even relatively mild stress can reduce immune response in both the young and the old. Stress reduction, correspondingly, increases immunocompetence.

Kiecolt-Glaser et al. (1985) found that geriatric residents of independent-living facilities who learned relaxation techniques had improved immune-cell activity and reduced production of antibodies in response to an introduced *Herpes simplex* virus (presumably reflecting improved control of virus replication and latency by the cellular immune response). In addition, Rodin (1986) showed that elderly subjects who learned skills for coping with daily stress had reductions in blood cortisol concentrations, presumably as a function of stress reduction, and they maintained the reductions 18 months after the intervention.

A final example is hemoglobin A_{1c}, which is an irreversibly glucosylated derivation of HbA. This form of hemoglobin is normally present in increased levels in diabetic patients and also appears to increase naturally with age (Arnetz et al., 1982; Graf et al., 1978). However, social factors can also affect blood glucose, and therefore HbA_{1c}, concentrations (Arnetz, 1984).

3

Principles of Gerontology

CONCEPTUAL CONTEXT OF GERONTOLOGY

Gerontology is the scientific study of the processes and problems of aging from all aspects—biologic, clinical, psychologic, sociologic, legal, economic, and political. Geriatrics is the branch of medicine that deals with the diagnosis, management, and prevention of medical problems associated with senility and senescence.

Although the terms "aging" and "senescence" are sometimes used synonymously, they are often differentiated by biologists. For example, Leopold (1978), a plant biologist, said that aging consists of "the processes associated with the accrual of maturity in time, whereas senescence may be defined as the deteriorative processes which are natural causes of death." The implication is that aging begins at birth.

Most gerontologists, however, are concerned primarily with age-related alterations in structure and function that occur after maturation. Maturation is usually defined as the achievement of sexual maturity and the adult stage of morphology and physiology. In addition, most gerontologists would not regard phenomena that were strictly coupled to chronologic time as fundamental, intrinsic aging processes. For example, changes (racemization) in amino acids in the ocular lens reveal how old an animal is, but do not

differentiate between the rate of aging of a short-lived mammal, such as a mouse, and that of a long-lived mammal, such as a human.

No one denies that developmental events before maturation are immensely important in setting the stage for the patterns of postmaturational aging. Thus, it is conceivable that perturbation of a particular aspect of development (e.g., the modification of some stem-cell pools by environmental agents) would have drastic effects on some aging processes decades later. For example, a depletion of the precursors of neurons of the substantia nigra could increase the probability of an early onset of Parkinson's disease. A change in the apparent thresholds for a great many other pathophysiologic phenomena that accompany aging might have, in part, such an etiology.

The aged population, however, is the primary focus of gerontology, and of this report, because it might be particularly vulnerable to many environmental agents as a result of normal age-related alterations in cellular structure and function, a general reduction in the ability to maintain physiologic homeostasis, and alterations acquired as a result of environmental exposures. Environmental agents conceivably act at any stage of the life cycle; precisely how they affect aging processes is not known, because the subject has not been adequately studied and because aging processes themselves have not been adequately described.

Variations in environmental exposure and genetic constitution make it very difficult to establish general indexes of aging, and a satisfactory analysis of aging processes will have to address the complexity of relationships of gene expression with the environment. Particularly in humans, genetic heterogeneity and environmental heterogeneity are such that probably no two individuals will ever be found to manifest aging in precisely the same fashion—even identical twins.

The genetic concepts of genotype and phenotype require definition. Johannsen (1909) originally defined the genotype, now commonly referred to as the genome, as the sum of the genetic information carried in the chromosomes of an organism. We now know of nonchromosomal inheritance (e.g., via mitochondrial DNA), and the term “genotype” is used to include all possible forms of genetic information that define a cell or organism and to refer to the particular form (allele) of a single gene or small group of genes. Until the advent of recombinant-DNA technology, the genotype

of an organism was deduced, in large part, from mating experiments. One can now directly isolate, clonally amplify, and analyze a particular segment of DNA.

Johannsen (1909) defined the phenotype as the sum of the observable properties (structural, biochemical, and physiological) of an organism or cell. One can refer to the senescence phenotype (or the aging phenotype) as the collection of attributes that are generally believed to characterize senescence (or aging). Gerontologists disagree about the extent to which age-related diseases should be considered integral features of that phenotype. One view is that each age-related degenerative or proliferative disorder has a pathogenesis that does not necessarily include an underlying component of intrinsic aging.

Another view is that many common age-related human diseases are ultimate expressions of underlying, slowly progressive, and insidious aging processes—for example, various forms of arteriosclerosis, including atherosclerosis and medial calcinosis; microvascular disease; glomerulosclerosis; osteoarthritis; osteoporosis; adult-onset diabetes mellitus; chronic obstructive pulmonary disease; presenile dementia; Parkinson's disease; cataracts; macular degeneration; and a variety of atrophies, hyperplasias, and neoplasias.

Phenotypic expression is the result of interaction between one's inherited genetic potential and the mosaic of one's environmental experience. Because of differences in inheritance and environmental experience, patterns of phenotype, including disease, vary. Life span, however, is a constitutional feature of a species, and, although environmental agents can readily modulate the life expectancy of populations, in most instances the life span is not influenced. Indeed, because life span appears to be under polygenic control that involves several aging processes, one would not expect a single environmental intervention to have global effects on it.

Advances in experimental genetics might permit critical tests of the structural and regulatory roles of allelic variation and mutation at specific genetic loci. The mouse *Mus musculus domesticus,* the worm *Caenorhabditis elegans,* and the fruit fly *Drosophila melanogaster* are the most-favored organisms for such research. For instance, the maximal life span of *C. elegans* is under direct genetic control (Johnson, 1987). In rodents, considerable progress is being made with dietary restriction as a means of extending

life span in experimental cohorts. These two approaches, the genetic and nutritional, might help to identify basic characteristics of aging and thus set the stage for a more rational exploration of environmental agents that promote aging.

Any number of toxic environmental agents can shorten life. One task of the gerontologist is to determine which might do so by influencing intrinsic aging processes. An agent that hastens the onset or increases the progression of a particular process or processes could be referred to as a "gerontogen." Such environmental agents would be expected to cause the premature onset or accelerated progress of functional decline and age-related disease, thus impairing the quality of life in the later decades. However, much more research on the fundamental mechanisms of aging will be needed before we can definitively evaluate potential environmental agents that influence aging processes.

Both longitudinal studies of environmental effects on aging in individual human subjects and large-scale cross-sectional studies of populations will be important in determining how aging and the environment are related. In longitudinal studies, observations are associated with different points in time. In cross-sectional studies, measurements of cause and effect are associated with one point in time. Cross-sectional studies are vulnerable to difficulties in interpretation, notably temporal cohort and selection effects. Figure 3–1 illustrates the differences one might find between comparable data collected in cross-sectional and longitudinal studies (in this case, data on cognitive function).

The evolution of changes with age has intrigued evolutionary biologists for at least 40 years. Aging is ordinarily not adaptively advantageous to the individual or to the species, but it seems likely that the changes are inevitable consequences of the action of selective forces (Charlesworth, 1980). They may be due to the accumulation of late-acting deleterious genes (Medawar, 1952) or to the action of genes that are beneficial early in life but harmful later (Williams, 1957). Various theories on the evolution of aging have been put forth, but the "disposable soma" theory of Kirkwood (1985), proposing that "fitness is maximized at a level of repair which is less than would be required for indefinite somatic survival," seems to encompass most alternatives.

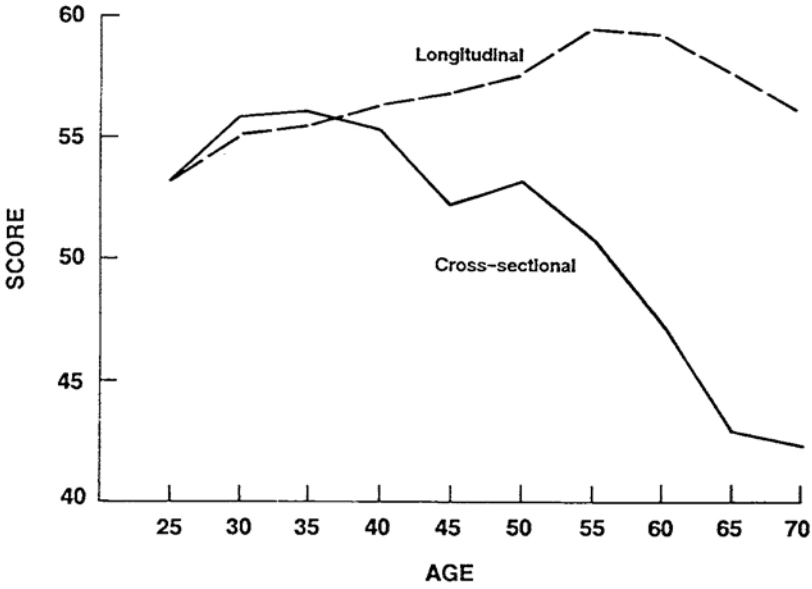

FIGURE 3–1 Estimates of cross-sectional versus longitudinal differences with age in performance on a test of cognitive function (the verbal meaning test) by human subjects of various ages. Reprinted with permission from Schaie and Willis (1986).

THEORIES OF AGING

Theories of aging can be grouped generally into two broad categories: those that invoke deterministic, or "programed," alterations in gene expression or gene structure, and those that invoke a variety of stochastic, or "random," alterations in the structure and function of macromolecules, cells, and organ systems.

There are limitations to this distinction, however, because stochastic alterations in individual cells can lead to predictable phenomena in the large population of cells. An example of the blurring of the deterministic and stochastic categorization is the use of terminal differentiation to explain the limited replicative life span of somatic cells (Bell et al., 1978; Martin et al., 1974)—that is, populations of cells cease dividing because they have differentiated into more specialized cells. For each individual cell, this differentiation is a random event. However, when viewed at the level of a population of many cells, the process appears deterministic.

Although primarily applied to the cell-culture model of cell aging (Hayflick and Moorhead, 1961), the idea of terminal differentiation might be applied to cohorts of stem cells in vivo (Martin, 1979). If the idea is valid, any environmental agent, such as retinoic acids (Strickland and Sawey, 1980), that depletes subsets of cells or alters states of differentiation might prove to be an important modulator of aging. Terminal differentiation would also have a large impact on cells undergoing rapid amplification, such as stem cells during early development.

The relative contributions of both classes of mechanisms are likely to be coupled to the reproductive strategy of the organism. Programed aging is characteristic of species with single massive episodes of reproduction (e.g., periodical cicadas). Placental mammals have ample opportunity for a variety of stochastic processes to take place during their long reproductive and postreproductive phases. The associated patterns of structural and functional decline can vary substantially both qualitatively and quantitatively and both among and within species.

It is beyond the scope of this report to describe and evaluate the many theories of aging that have been developed over the last several decades. (See Warner et al., 1987, for a recent monograph on the subject.) For our purposes, however, it is useful to cite and summarize a few examples, in order to illustrate how a suitable theoretical framework could serve as a rationale for the exploration of the impact of particular classes of environmental agents on particular processes of aging, age-related diseases, or special susceptibilities of aged people.

Deterministic Theories

Developmental Switches in Gene Expression

Senescence does not appear to be programed in the same way as development—that is, regulated by a series of linked gene actions, whose primary result is to produce a limited life span. Only under special conditions in organisms that have a single episode of reproduction in their lifetime (semelparous organisms) can senescence be seen to be directly "programed." Senescence does not seem to be driven by the sequential, systematic turning on and off of new genes; indeed, there is little change in the

transcripts that are made throughout the organism's adult life (Rothstein, 1982).

This does not mean that modulation of transcriptional activity or gradual loss of tight control of gene transcription plays no role in senescence, and detailed investigation of environmental agents that alter gene expression in a way that suggests an impact on specific aspects of the aging phenotype might be warranted. No examples are yet known, although such agents as amanitin, which perturbs transcription, and cyclohexamide, which perturbs translation, have potential utility.

Neuroendocrine-Cascade Theories

Finch and Landfield (1985) reviewed a group of theories that can be classified as neuroendocrine-cascade theories. An excellent example is the glucocorticoid-cascade hypothesis of aging proposed by Sapolsky et al. (1986b).

The basis of the hypothesis is the finding in rats that basal plasma corticosterone concentrations increase with age, and that although the increase in plasma corticosterone in response to stress does not change with age, the return to basal concentrations after the removal of stress is markedly delayed with age. The reason for the age-related changes is a gradual impairment in negative feedback control of plasma glucocorticoid concentration themselves (Sapolsky et al., 1986a). The loss in sensitivity is related initially to a loss of corticosterone receptors in some hippocampal neurons and ultimately to a loss of hippocampal neurons themselves (Sapolsky et al., 1983a). Moreover, it is the cumulative exposure to glucocorticoids that is responsible for the decrease in glucocorticoid receptors and for the loss of the hippocampal neurons themselves (Sapolsky et al., 1986b).

The net result is the emergence of hyperadrenocorticism that has been largely caused by the stresses encountered during the rat's lifetime. Hyperadrenocorticism might be responsible for a host of age-associated problems, such as immunosuppression, muscle atrophy, osteoporosis, and glucose intolerance. Evidence exists that hyperadrenocorticism, at least in part, underlies age-related disease in rodents (Riley, 1981b; Sapolsky and Donnelly, 1985).

Although the theory deserves to be further tested experimentally, a major problem is that the changes noted in adrenocortical function in rats with advancing age have not been found in most

other species. There is no evidence of such an occurrence in normal human aging, although no systematic investigations have been carried out. Such theories have special implications for toxicologists because they raise the possibility that global effects on aging would follow exposure to particular environmental agents (e.g., stress, glucocorticoids and their analogues, agonists and antagonists of particular receptors, and specific neurotoxins).

Stochastic Theories

Intrinsic Mutagenesis Theory

Burnet (1974) summarized arguments that cumulative damage to the genetic material causes aging in mammals. According to this proposition, short-lived mammals are more prone to develop somatic-cell mutations than long-lived mammals. That could occur, for example, if the DNA polymerases of short-lived species were comparatively error-prone or if their various DNA repair mechanisms were comparatively inefficient. Support for the theory comes from observations of a positive correlation between species longevity and the efficiency of the cellular repair of DNA damage induced by ultraviolet light (Francis et al., 1981; Hart and Setlow, 1974).

There is controversy, however, about the extent to which such gene mutations accumulate in the tissues of aging mammals (Horn et al., 1984; Inamizu et al., 1986; Trainer et al., 1984). Various types of chromosomal mutations do accumulate with aging, however (Brooks et al., 1973; Crowley and Curtis, 1963; Curtis and Miller, 1971; Martin et al., 1985). Chromosomal mutations could arise from different mechanisms, including chromosomal breaks initiated by free radicals (Nichols and Murphy, 1976), rearrangement after gene amplification (Schimke et al., 1986), and insertional mutagenesis mediated by transposons (jumping genes) (Collins and Rubin, 1984; Shapiro, 1983).

Genomic instability could also result from mechanisms not associated with classical forms of somatic-cell mutation. By definition, the latter involve alterations in the primary structure of the genetic material (including various rearrangements), as well as changes in the amount of the genetic material. Stochastic changes in gene expression, for example, might be attributable to perturbations of chromatin configuration or of the patterns of DNA

methylation. This theory has obvious implications for categories of environmental agents (physical, chemical, and viral mutagens) that could accelerate the aging processes.

Protein-Synthesis Error Catastrophe

Orgel (1963, 1970) argued that mistakes in the synthesis of proteins that participate in the machinery of protein synthesis, at either the transcriptional or translational level, have the potential, through a positive-feedback loop, to cause a general exponential loss in the fidelity of protein synthesis. That loss could lead to an error catastrophe in which a large proportion of proteins in aged cells would be abnormal in structure and function. Because the abnormal proteins would be expected to include various DNA-dependent DNA polymerases and DNA repair enzymes, the protein-synthesis error-catastrophe theory is among the theories of aging that predict the accumulation of somatic mutations. Moreover, the theory predicts a predominance of point mutations (missense and nonsense mutations) and an accumulation that exhibits exponential kinetics near the end of the natural life span. Among the many host genetic loci that might modulate the rates of development of errors in protein synthesis, loci that control the quality and quantity of scavenger proteases would be particularly important, in that an error catastrophe could be averted by preventing the inheritance of the abnormal protein-synthetic machinery in sequential generations. Many experiments have attempted to support or refute this mechanism of aging, but none can be considered definitive, especially because few studies have addressed the problem in postreplicative cells in vivo (e.g., neurons). The bulk of the evidence, however, argues strongly against the general validity of the theory (Filion and Laughrea, 1985; Gallant, 1981; Rothstein, 1982).

From the toxicologist's viewpoint, the theory would provide a rationale for examining the effects of such agents as amino acid analogues, a number of which exist in large concentrations in plants. For example, the concentration of canavanine (an arginine analogue) constitutes about 1.5% of the dry weight of alfalfa sprouts and alfalfa seeds (a widely used natural, or organic, foodstuff) (Bell, 1960) and is toxic to primates (Malinow et al., 1982).

Any chemical agent that affected the fidelity of protein synthesis would be worth examining in more detail, for example,

antibiotics such as streptomycin that perturb ribosomal function and toxins that could affect protease function.

Free Radicals

Harman first proposed the free-radical theory of aging in 1954 (reviewed by Harman, 1981). Free radicals are continuously being generated in living systems through the action of ionizing radiation and a wide variety of nonenzymatic and enzymatic reactions. In mammals, the major source of free radicals is the consumption of oxygen by mitochondria for oxidative metabolism; the superoxide radical is an example of the kind of free radical generated (Nohl and Hegner, 1978).

The damage caused by these radicals includes oxidative alterations in long-lived molecules, such as DNA or collagen (Harman, 1981; LaBella, 1965); oxidative degradation of mucopolysaccharides (Matsumura et al., 1966); generation of lipofuscin (Norkin, 1966); and alterations in biologic membrane characteristics (Hegner, 1980). However, cells have defenses to protect them from damage by free radicals, such as antioxidants (e.g., tocopherols and carotenes) (Klebanoff, 1980) and peroxidases and superoxide dismutases (Fridovich, 1977), as well as repair mechanisms, such as those for DNA (Nichols and Murphy, 1977).

Although the free-radical theory is provocative, hard evidence to support it is lacking. One approach to testing the theory has been to study the effects of dietary antioxidants on the longevity of rodents. In some of the studies, life expectancy was increased, but life span was not (Harman, 1981). Moreover, many of the studies were flawed in that they did not measure food intake or food intake was reduced (Masoro, 1985).

Another line of evidence used to support the free-radical theory is the claim that life-prolonging food restriction lowers the metabolic rate (Harman, 1981). Recent work has shown, however, that food restriction can increase life span without decreasing the metabolic rate (McCarter et al., 1985). It is conceivable, however, that dietary restriction could decrease the flux of active oxygen species independently of metabolic rate. In any event, the free-radical theory has important implications for investigating environmental effects on aging, notably, the potential of dietary and chemical agents to alter the flux of active oxygen species.

Posttranslational Glycation of Proteins and DNA

Cerami (1985) proposed that glucose is a mediator of aging. He suggested that a loss of biologic function due to the nonenzymatic reaction of glucose with proteins and nucleic acids (the glycation of proteins and nucleic acids), yielding advanced glycosylation end products, is a basic mechanism of aging.

The glycation of proteins and nucleic acids begins with reaction of an amino group with the aldehyde group of glucose to form a Schiff base. Once formed, the unstable Schiff base of glucose can undergo an Amadori rearrangement to form a more stable product, the Amadori product (Mortensen and Christophersen, 1983). The Amadori product can undergo a series of dehydration steps and rearrangement to yield brown, fluorescent pigments (Monnier and Cerami, 1981), called advanced glycosylation end products by Cerami (1985). The end products cross-link proteins and nucleic acids and thereby cause loss of biologic function (Cerami, 1985). The chemical nature of the advanced glycosylation end products has not been fully elucidated, but one appears to be 2-(2-furoyl)-4(5)-(2-furanyl)-1*H*-imidazole (Pongor et al., 1984). The rate of formation of advanced glycosylation end products is increased as the concentration of glucose and time of exposure to glucose increase (Monnier et al., 1984).

Although this theory of aging is intriguing, little hard evidence supports it. Cerami noted that the complications of diabetic patients are often put forth as a paradigm of aging. Clearly, those complications could also be related to other alterations in glucose metabolism or to insulin action, rather than to glycation reactions themselves. Nevertheless, Cerami's glycation theory warrants further testing. One avenue of approach is the use of such compounds as aminoguanidine, which prevent the protein cross-linking action of glucose (Brownlee et al., 1986). Another is the judicious use of the food-restriction paradigm (Masoro, 1985).

Thymic Involution as a Pacemaker of Immunosenescence

The morphologic and functional involution of the thymus gland is a particularly early and striking precursor of immunologic aging in humans and, indeed, in all mammalian species thus far investigated (mostly rodents). In humans, the loss of cellular mass of the thymus begins at sexual maturity and is complete by the age

of around 50, when the thymus retains only 5–10% of its maximal mass. Thus, the striking involution of the thymus gland during the first half of life can be largely related to the altered form and function of the immune system observed during the second half of life. These alterations have been well documented in humans and experimental animals. Particularly notable are alterations in T lymphocytes.

Two functions of the thymus gland have been recognized: the production of a family of polypeptide hormones and the maturation of T-lymphocyte precursors from the bone marrow. Thymic hormones are important in the differentiation of prethymic and postthymic lymphocytes. In humans, thymic hormone activity in serum is maintained from birth until the age of 20–30 and then declines (Weksler, 1986). Thymic hormone can no longer be detected in healthy normal humans over 60 years old. It has been suggested that the low activity of serum thymic hormone is due to the presence of inhibitors (Weksler, 1986).

Immature lymphocytes from the bone marrow enter the cortex of the thymus gland. With age, fewer immature lymphocytes enter the thymus, and the gland loses its capacity to facilitate the differentiation of these cells (Weksler, 1986). Perhaps as a consequence of these events, immature T lymphocytes are found in increased numbers in the blood of elderly humans (Weksler, 1986). Thus, with age, serum thymic hormone activity declines, and the percentages of immature lymphocytes in the thymus gland and in the peripheral blood increase.

Environmental agents with the potential to modulate those events early in life, either centrally (e.g., specific neurotoxins) or peripherally (e.g., exposure of the thymus to ionizing radiation), might be expected to have far-reaching effects on the patterns of immunosenescence in later years.

BIOMARKERS OF AGE OR AGING

A biomarker of aging is a biologic event or measurement of a biologic sample that is considered to be an estimate or prediction of one or more of the aging processes. The concept has drawn considerable attention in recent years and is the subject of two extensive publications (Ludwig and Masoro, 1983; Reff and Schneider, 1982). Most recently, a 1986 workshop on the subject sponsored by the Task Force on Environmental Cancer and Heart

and Lung Disease (Baker and Rogul, 1987) discussed biomarkers of aging.

The fascination with the concept of biomarkers of aging stems from their immense potential usefulness (e.g., in the context of this report, to assess the effects of environmental agents on aging processes) and the superficial evidence that they are easy to develop. As an illustration of the latter idea, consider physiologic systems as potential markers. Most physiologic systems change with age, and the extent and rate of such changes differ among individuals.

Why, then, is there controversy about biomarkers of aging? The major reason is that the nature of aging itself is unknown. Even the number of primary aging processes is debatable. A few investigators believe that there is a single primary aging process and that all other aging events are secondary or even further removed from it. Most believe that there are several primary aging processes, none of which has been clearly identified. And a few believe that aging is not the result of primary processes at all, but rather is due to subtle changes in interactions of the components of the homeostatic regulatory processes. With so little knowledge about the nature of aging, there is no central standard by which to judge the validity of any of the many biomarkers of aging that have been proposed.

Another aspect of the controversy is related to the different uses contemplated for biomarkers of aging. The uses can be categorized as estimation of an individual's chronologic age, estimation of an individual's biologic or physiologic age, prediction of the occurrence of an age-associated disease, prediction of impending death, and prediction of the life span of a species. Each of these uses should be considered in regard to its relevance to aging.

A biomarker used to estimate chronologic age is of value only when age is not known. The major, if not the sole, use of such a biomarker is to estimate the ages of animals in a colony of animals of unknown age. A good biomarker for this purpose seems to be amino-acid racemization in structural proteins sequestered from metabolic turnover (Bada and Brown, 1980).

The problems of biomarkers proposed to estimate the biologic or physiologic age of an individual are related to the facts that different systems in the same individual can age independently (e.g., the occurrence of grayness of the hair bears no relationship to age-associated deafness) and an individual's rate of aging might

not be constant (Costa and McCrae, 1980). Of course, most investigators interested in determining physiologic age have recognized the pitfalls of assessing it on the basis of a single physiologic system and have turned to examining several systems simultaneously, using either multiple regression analysis (Furukawa et al., 1975) or profile analysis (Borkan, 1978). Costa and McCrae (1985) have pointed out that there is no evidence that such analyses provide better information about functional age than does chronologic age itself.

Biomarkers used to predict the occurrence of an age-associated disease are commonly considered to be risk factors for the disease in question. Increased arterial blood pressure is a risk factor for stroke (Kannel, 1985), and the blood concentration ratio of total cholesterol or arterial low-density lipoprotein to high-density lipoprotein is a risk factor for coronary disease (Gotto, 1986).

These risk factors are, at least in part, linked to stroke and coronary arterial disease, respectively, by promoting the atherosclerotic process (McGill, 1977). However, the relation of atherosclerosis to aging is not clear. That is, do aging and atherosclerosis merely share the same time frame or are they causally related? The uncertainty is similar in the case of other age-associated diseases. Thus, it is questionable whether predictors of the occurrence of age-associated disease are valid biomarkers of aging.

Predictors of impending death have been viewed as biomarkers of aging. For example, impairment of pulmonary function predicts a mortality rate over the next 4–20 years that is higher than in those lacking the impairment (Beaty et al., 1982). But cardiovascular disease and cancer, not pulmonary disease, are the major causes of death. Does that mean that impairment of pulmonary function is a biomarker of aging, or is it merely a predictor of two diseases, cancer and cardiovascular disease?

It is not yet possible to answer this question, but changes in mortality in the United States during the last 150 years favor the latter. For instance, life expectancy and the median length of life in the United States have markedly increased since 1840 (U.S. Bureau of the Census, 1984). Most of the increase in longevity is related to the control of infectious diseases by technology and medicine, not to the aging processes. The change in mortality characteristics is an index of the extent to which protection from environmental hazards has enabled the population to age. It is in accord with this view that, although life expectancy has markedly

increased in the United States during the last 150 years, the life span of Americans has not changed. This is strong evidence that changes in mortality characteristics might have little to do with aging processes.

Predictors of the life span of a species potentially serve as valid biomarkers of aging. Changes in life span are likely to be due to changes in the rate of aging; it is possible that the life span of a species can be increased *only* by retarding the aging processes. Few manipulations are known to extend the life span (Sacher, 1977). Low environmental temperature, food restriction, and genetic manipulations have that effect in poikilotherms, and food restriction has that effect in rodents, which are the only mammals in which lifespan extension by manipulation has been rigorously demonstrated.

Food restriction in rodents retards many age-related physiologic changes and age-associated diseases (Masoro, 1985), and all these are potential biomarkers of aging. The challenge is to determine whether a particular physiologic or disease process influenced by food restriction is indeed a biomarker of aging or is related to food restriction in some other way. Exploring this question will require the use of more than one manipulation that affects the life span of a particular species. That is, if a physiologic or disease process can be retarded similarly by several manipulations that extend the life span of a species, this would strongly indicate that the physiologic or disease process in question is a biomarker of aging. Thus, research aimed at identifying such manipulations should have a high priority if valid biomarkers of aging are to be developed. Such biomarkers are essential to the testing of the effects of environmental agents on the aging processes.

ALTERED SUSCEPTIBILITY OF THE AGED

The elderly are in many ways showing more individual variation in biologic responses than the young. The variation probably has more influence on their intrinsic vulnerability to the effects of toxic substances than physiologic aging and precludes broad generalizations about their susceptibility. Nevertheless, both the increased incidence of disease in the elderly population and the normal physiologic changes that occur with aging in the absence of disease can make this population more vulnerable to environmental insults.

Although only a few studies of altered response to environmental agents in aging humans have been conducted, they show that older people tend to respond to drugs differently from younger persons, both qualitatively and quantitatively, and to have a higher incidence of adverse or idiosyncratic drug reactions (Conrad and Bressler, 1982). Thus, it is reasonable to assume that the elderly would tend to respond differently to other environmental factors. For example, "experiments of nature" (Chapter 7) such as the air-pollution incidents in London, the Meuse River Valley in Belgium, and Donora, Pennsylvania demonstrated that the most vulnerable people were the elderly, probably because of the normal age-associated decline in cardiopulmonary function, and others with pre-existing disease of the cardiopulmonary system. Moreover, inasmuch as response to pathogens depends on immune response, the susceptibility of older persons to diseases caused by pathogens is increased through age-related reductions in immune function.

One of the most important factors affecting the elderly population is the fact that multiple diseases are the rule, rather than the exception. Superimposed on past injuries, illnesses, and operations can be a variety of chronic disorders, such as cataracts, pernicious anemia, osteoarthritis, osteoporosis, atherosclerosis, and diabetes. Malignancy, stroke, Parkinson's disease, dementia, and fracture of the femur all have increased incidences in the elderly. In addition, chronic illness often leads to other complications in the elderly, including thromboembolism, dehydration, urinary tract infection, pressure sores, hypostatic pneumonia, and immobility contractures.

The elderly often manifest an altered response, both physical and psychologic, to disease. In geriatric patients, infection is often associated with mild tachycardia and mental confusion or other nonspecific symptoms. Fever, leukocytosis, lymphadenopathy, and lymphangitis can be minimal or absent. The elderly seem to be less sensitive to pain and more stoical. Angina is often atypical, and painless myocardial infarction is more common in the elderly than in younger patients.

Superimposed on the overt diseases so prevalent in the elderly are important and sometimes subtle physiologic changes that occur with normal aging. For example, age-related changes in the physiologic processes that control absorption, distribution, metabolism,

and elimination of drugs have been shown to affect drug responsiveness in the elderly in some cases and might reasonably be expected to influence response to other toxic agents.

Physiologic changes that are associated with age often alter one's susceptibility to adverse health effects, and a person's ability to withstand various environmental exposures is often compromised as a result. Many of the changes are well documented, and not all are associated only with the elderly. For example, changes in the immune system that affect a person's ability to fend off disease occur throughout the life cycle. Involution of the thymus is probably the most striking anatomic change in the immune system that accompanies aging; it begins at sexual maturity and is complete by the age of 45–50. The striking increase in the mortality associated with influenza in the elderly is one consequence of this decline in host defense.

Aging is also associated with important changes in the nervous system that can allow previously masked neurotoxic disorders to become manifest. It is generally believed that altered neural function occurs only after structural and functional redundancy has been expended. For example, a parkinsonian state appears only after a considerable loss of neurons in the substantia nigra; this might occur both as a consequence of aging processes and after exposure to particular chemical substances (i.e., *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPTP). More-specific examples of age-associated diseases and physiologic changes and their association with the environment are discussed in Chapter 6.

The several changes in human cutaneous anatomy and function now recognized to occur with age can increase the vulnerability of the elderly to both chemical and physical environmental insults. For example, altered barrier function of the stratum corneum (horny layer) of the skin in elderly people can increase percutaneous absorption of drugs and other chemicals (Roskos et al., 1986). The important role of the epidermis in detoxifying percutaneously absorbed chemicals has only recently been recognized (Das et al., 1986) and has not been examined with regard to age.

Decreases in dermal vascular area (Gilchrest et al., 1982a; Montagna and Carlisle, 1979) and vasoreactivity (Gilchrest et al., 1982a; Grove et al., 1981) in old skin might slow dermal clearance of topically absorbed substances (Kligman, 1979) and diminish the body's thermoregulatory capacity. Those effects would contribute

to hypothermia and heat stroke during exposure to extreme temperatures (Besdine, 1980).

Age-associated loss of epidermal Langerhans cells (Gilchrest et al., 1982b) is presumed to impair recognition of foreign antigens, possibly including malignantly transformed cells, in the skin. The well-documented loss of melanocytes (pigment cells)—10–20% of the residual cell population per decade (Gilchrest, 1979)—is postulated to decrease the body's protection against injurious ultraviolet radiation. In combination with age-associated reductions in immunocompetence (Schneider and Reed, 1985), this loss might predispose the elderly to photocarcinogenesis. A decrease in the vitamin D precursor in the epidermis and a decrease in photoconvertibility (MacLaughlin and Holick, 1985), in combination with a dietary lack of dairy products and a lack of regular sun exposure, might easily render the elderly deficient in vitamin D and lead to clinically important osteomalacia (Nordin et al., 1980).

Finally, the well-documented age-associated decrease in sensory perception, including pain perception (Procacci et al., 1974), unquestionably renders the elderly more vulnerable to some types of environmental injury.

4

Principles of Toxicology in the Context of Aging

The science of toxicology has a dual nature. It is the study of mechanisms by which environmental agents exert their toxic effects, and it is the empirical definition of the magnitude of toxicity of such agents and the risk they present to exposed human populations.* Toxicology, more than most disciplines of biology, depends on comparison of experimental results with large data bases acquired through the application of standard test protocols to large numbers of chemicals and types of radiation.

To study both the possible exacerbation of aging processes by environmental agents and the potential of increased toxicity for elderly people, mechanisms of aging must be considered with respect to their similarity to mechanisms of toxicity of known toxic agents. In addition, tests that will permit the screening of environmental agents for their potential to interact with aging processes or to present an increased hazard to the aged will need to be identified. Once such potentially interacting agents are identified, they must be evaluated in whole-animal systems that are appropriate surrogates for human response. The species selected must not only be

*For detailed descriptions of general toxicology, see Hayes (1982) and Klaassen et al. (1986). More specifically, Williams et al. (1987) have discussed the toxicologic perspective of the relationships between aging and the environment.

appropriate with respect to aging, but must also be representative of human response for any particular chemical tested. Identification of common mechanisms and creation of test systems must both take place in the context of the existing data bases.

Some people view aging as a toxic process, and indeed some age-related functional changes mimic toxic processes. Aging is clearly associated with alterations in homeostasis and in organ and cellular integrity; many changes of aging resemble those induced by toxicants. Thus, aging might well be associated with alterations in metabolic states that lead to the body's formation of toxic molecules or to alterations in the normal regulation of concentrations of various natural substances in the body. Toxicologic research has found that even the most unlikely substances can be implicated in tissue damage if their concentrations deviate enough from normal.

Nutrition underscores the usefulness of considering aging as a toxic end point. For example, both deficiency and excess of vitamin B_6 can lead to neurologic damage (and these changes superficially resemble those accompanying aging).

Another reason that aging can be usefully explored as a toxic process in its own right is that aging itself is probably the primary cause of or a cofactor in all age-associated disease. Furthermore, aging cannot be readily arrested and is present during any whole-animal experiment. Thus, all toxic processes induced by external agents can interact with aging processes, and the possible impact of this interaction would be greater with chronic exposures or toxic effects whose latency includes a substantial portion of the life span.

If aging is a toxic process, can it be mimicked by chemical or physical agents? The full answer to the question occupies much of this discussion, but the simple answer is that many agents present in the environment can, at high doses, induce some pathologic changes and physiologic deteriorations similar to those observed in the aged. This is a limited form of mimicry, because a given agent generally produces only a few aspects of aging in only one tissue (or at most several). Only a few agents, such as ionizing radiation, cause damage throughout the body.

The absence of universal mimicry of aging by toxic agents, even in a given tissue, is an important observation that must not be overinterpreted. A toxic agent might produce molecular lesions similar to aging-induced lesions. But the experience of toxicology is that the manifestation of molecular or cellular damage at the

tissue level is not rigorously specific to the toxic agent. Diverse agents that are believed to produce the same kinds of damage at the cellular or molecular level sometimes induce different kinds of damage at the tissue level. Conversely, diverse toxic agents sometimes produce similar pathologic effects; that is, the processes that manifest some effects can be triggered by different agents.

All tissues deteriorate during aging. The observation of the breadth of the effects of aging requires a similarly broad toxicologic approach. Special attention must be directed toward evaluating data bases for long-term whole-animal bioassays, because these toxicologic evaluations have been used to evaluate the results of prolonged exposure to toxic agents at low concentrations, including environmentally important agents, and they constitute a major tool for quantitative risk assessment.

Neurotoxicology and immunotoxicology should also be emphasized. Most environmental agents have not been screened for neurotoxic and immunotoxic effects, and some neurologic and immunologic deficits of unknown etiology are observed in a large proportion of the aged.

From the toxicologic perspective, two general problems present the greatest concern in the consideration of environmental relationships with aging. First, the mechanisms of aging are unknown, so toxicologic methods of detecting perturbations in the essential biology of the aging processes are not readily feasible. Second, the empirical approach is thwarted because there are no comparative data to validate any test proposed to detect agents that specifically affect aging or the aged.

One approach to the two problems is to discern the mechanisms of aging and search for agents that specifically affect aging or the aged. Much effort has been expended on the former; great resources would be needed for the latter. One purpose of this report is to propose the most economical and scientifically sound plan for the overall approach to the two problems.

In addition to aspects of conventional toxicology that appear most relevant to the relationship of chemical toxicity and aging, three new types of questions must be addressed:

- How can agents that might interact with the aging processes to increase or hasten the appearance of pathologic effects or reduced resilience in the aged be identified? Certainly, the stan

dard long-term bioassay could detect large age-associated pathologic changes, but it is not clear whether it can mimic exposures that are inherent in the human environment and absent from the pristine laboratory environment of the surrogate animal.

- How cam acute or subacute exposures in utero, during development, or during maturity that sensitize the exposed to other agents be identified? For example, in multistage carcinogenesis, exposure to a cancer initiator can sensitize animals to later exposure to a cancer promoter. The problem of whether similar mechanisms induce any of the wide spectrum of pathologic effects observed in the aged is extremely difficult to approach with standard toxicologic tests.
- How can environmental agents, particularly pharmaceuticals, that hold increased hazard for the aged be identified? Most toxicity is measured in young animals, so a more specific question is whether testing performed in young animals can predict the response of old animals. If the responses of young and old animals to a given agent are qualitatively similar, but quantitatively different, the application of a safety factor might permit the data from young animals to be modified for predicting risk in old animals. If the mechanism of action differs, such extrapolation would not be possible; testing with old animals, and the attendant expense and absence of comparative data, would then be necessary.

The remainder of this chapter summarizes the general concepts of toxicology (i.e., absorption, distribution, metabolism, and elimination), the effects of chemicals in the body as a function of age, mechanisms of toxicity at various levels of physiologic organization, and the importance of pharmacogenetics, biomarkers, and toxicity testing.

CHEMICAL FATE AND EFFECT

Chemicals enter the body by inhalation, ingestion, and contact with the skin. They can act at the local site of contact, or they can be absorbed, enter the bloodstream, and be transported to act at other sites. Toxic agents are eliminated from the blood by biological transformation and by excretion or accumulation at various sites. The liver is active in biotransforming toxic substances; however, enzymes in the kidneys, lungs, gastrointestinal tract, skin, and other tissues can also metabolize toxicants. Some

toxicants accumulate in organs or tissues, where they might or might not produce toxic effects. Most toxicants are eliminated in the urine via the kidney or in the bile via the liver, although some volatile toxicants can be eliminated in the exhaled air via the lungs.

Most of the research on the effects of old age on the absorption, distribution, metabolism, and elimination of chemicals has focused on drugs, rather than on toxic environmental substances. Many toxic chemicals are converted to less toxic, or in some cases more toxic, chemicals by the same pathways that are responsible for the biotransformation of drugs, so data on drugs have relevance for toxicologic concerns. For information on aging and drug disposition, several comprehensive reviews of geriatric pharmacology are available (Greenblatt et al., 1982; Schmucker, 1978, 1985; Vestal and Dawson, 1985).

In contrast with the data on pharmaceutical agents, which are based on studies of both animals and humans, virtually all the data on toxicants have been obtained from experimental animals. Furthermore, as documented in a monograph by Calabrese (1986), the human data and many of the animal data are related to neonatal and young subjects. Of particular interest is the possible influence of age on the detoxification of carcinogens, on the conversion of procarcinogens to carcinogens, and on the interaction of carcinogens with potential inducing agents.

Age-related changes in carcinogen metabolism in young and old animals have recently been reviewed by Birnbaum (1987), who concluded that the available data were both conflicting and sparse. The results of metabolic studies depend on substrate, species, gender, and even strain. Age-related changes in the monoxygenase components of nonhepatic tissues have hardly been examined. Thus, although it has been tempting to hypothesize that age-dependent changes in carcinogen metabolism might contribute to the increased incidence of cancer with aging, this is an oversimplification. For specific compounds, biotransformation might differ with age in a given tissue, but the differences might not result in a greater concentration or longer duration of action of carcinogenic chemicals or reactive metabolites at vulnerable target sites.

Although many, but not all, animal studies have suggested that aging is not associated with a loss of the capacity of oxidative metabolism to respond to inducers—such as barbiturates, poly

cyclic hydrocarbons, and steroids—the question has received less attention from clinical investigators. In addition to metabolism, such toxicokinetic measures as absorption, distribution, and renal and biliary excretion and toxicodynamic determinants of tissue sensitivity can change with age. Thus, an increased carcinogen sensitivity in older persons might result from complex interactions of many processes that have not been investigated systematically in either humans or animals.

Awareness of the effects of age on the absorption, distribution, metabolism, and elimination of drugs can provide insight into the mechanism of altered response to chemicals in general. Studies of age differences in pharmacodynamics (biochemical and physiologic effects of drugs and their mechanisms of action) must take into account possible age differences in pharmacokinetics (absorption, distribution, metabolism, and elimination). For example, studies generally show that the elderly are more sensitive to the depressant effects of neuroactive drugs (such as diazepam) (Giles et al., 1978; Reidenberg et al., 1978) and the analgesic effects of narcotics (such as morphine) (Bellville et al., 1971; Kaiko, 1980); in contrast, the in vivo sensitivity of the heart to isoproterenol and its antagonist propranolol appears to decline with age (London et al., 1976; Van Brummelen et al., 1981; Vestal et al., 1979). There is also evidence that cellular biochemical responses to some drugs are altered with aging.

Absorption

Absorption is the major process by which toxicants are transported across body membranes. The main sites of absorption of toxic agents are the skin, lungs, and gastrointestinal tract. Many toxicants can be absorbed through the skin and enter the bloodstream. Chemical or physical injury and other circumstances can increase the skin's permeability. Toxicants that are absorbed by the lung are in the form of gases or solid or liquid aerosols. Absorption can be rapid and complete because the lungs have a large surface area and a blood supply that is close to inhaled air in the alveolae. A variety of environmental toxicants enter the food chain and are absorbed from the gastrointestinal tract. Many factors alter the gastrointestinal absorption of toxicants, including

gastrointestinal motility, the physical and chemical properties of the toxicant, and gastrointestinal content.

A number of physiologic alterations associated with old age might be expected to affect absorption from the gastrointestinal tract. They include an increase in gastric pH, a reduction in intestinal blood flow, a reduction in the number of absorbing cells, a decrease in gastrointestinal motility, and a slowing of gastric emptying. An increase in gastric pH might affect the ionization and solubility of some substances, but there are few specific data on the range of pH values that can be encountered in the elderly population and the effects of increased pH on bioavailability. Older people have reduced gastrointestinal motility and slower emptying, which might be expected to decrease the rate of absorption.

Some studies have shown an increase in the time to peak plasma concentration after oral drug administration. This has only minor clinical importance because the extent of absorption did not differ between young and old subjects. Although the data are sparse, most studies on drug absorption in the elderly do not demonstrate a marked effect of age on the rate and extent of absorption.

Distribution

Once a toxicant enters the bloodstream, it is available for distribution throughout the body. Only free toxicants—those not bound to plasma proteins—are able to enter other sites. Such binding is of particular concern to toxicologists and medical scientists, because toxicants bound to those proteins can be displaced by other chemical agents and, once released, go to target organs and produce injury there.

The distribution of toxicants depends on their ability to cross cell membranes and on their affinity for various body components. Toxicants vary widely in these two characteristics. Some do not readily cross cell membranes and therefore have restricted distribution. Others bind to various sites in the body, such as fat, liver, kidneys, or bone. The major toxic action of a toxicant might take place where it binds, but often it does not. In fact, binding sites often serve as storage depots whose existence helps to protect the body from the toxic action.

A variety of age-related changes can alter the volume of distribution of substances throughout the body. Body composition

is one of the most important. Total body water (both in absolute terms and as a percentage of body weight) is reduced by 10–15% between the ages of 20 and 80 years; lean body mass in proportion to body weight is also diminished with age, and body fat is increased. These changes can be predicted to cause higher blood concentrations of substances that are distributed mainly in body water or lean body mass. Alterations in body fat can result in the accumulation and prolongation of action of highly lipid-soluble substances.

In addition, a decrease in serum albumin in the aged means that greater amounts of substances that bind to serum albumin, such as the anticonvulsant phenytoin, will be free to diffuse into body tissue. In contrast, serum a_1-acid glycoprotein is increased in the elderly, and that reduces plasma-protein binding of weak bases, such as the antidepressant imipramine and the antiarrhythmic drug lidocaine. Thus, because free-drug concentration is an important determinant of drug distribution and elimination, altered plasma-protein binding might be one cause of altered pharmacokinetics in the aged. Available data suggest, however, that disease and immobility have greater effects on albumin concentration than age itself.

Metabolism and Elimination

Some chemical agents that enter the body can remain as intact molecules, but many are biologically transformed by metabolic processes. Metabolic processes might involve simple and reversible chemical or physical interactions that primarily affect transport throughout the body and across membranes. In other cases, metabolic processes can substantially alter the chemical nature of the toxicant and create a more toxic or less toxic agent. The metabolic processes can facilitate elimination from the body.

It has been useful to consider the metabolic processes as being of two types. The first includes processes of oxidation, reduction, or hydrolysis that primarily alter or add functional (reactive) moieties to the molecule in question. The second includes chemical reactions of pre-existing or newly formed functional groups on the molecule with various endogenous chemicals (such as amino acids, sulfate, and glucuronic acid) to form conjugates, or new chemicals.

The biosynthesis of these products often alters lipid or water solubility and ionization characteristics in ways that promote their secretion and excretion.

The major routes for elimination of chemical agents from the body are from the kidneys to urine, from the liver to bile to feces, and from the lungs to exhaled air. Minor routes include secretions from the body—such as sweat, tears, saliva, mucus, digestive juices, and milk—and hair, nails, and desquamated epithelial tissue. As mentioned above, such factors as age and disease state that interfere with kidney function or biliary excretion in the liver can affect the toxic potential of chemicals in the body.

The kidney's excretory mechanisms include filtration in the glomeruli and secretion and reabsorption in the renal tubules. Elimination via the kidneys is thus a function of blood flow to the kidneys, molecular volume relative to pore size of the glomerular filter, physicochemical characteristics of the molecule that affect membrane transport, and enzymatic or other systems that might activate or facilitate secretion and reabsorption. Chemicals that bind to large molecules, such as plasma proteins, might not be eliminated by filtration and might be retained in the body for long periods.

The liver is especially important as a route of elimination of chemicals that are ingested, because most of the blood from the gastrointestinal tract goes through the liver on its way to the general circulation. The liver is in a unique position to metabolize a chemical through its enzymatic systems and to secrete the metabolites into the bile. Bile empties into the intestines, where the chemical can either be further altered and reabsorbed or be eliminated in the feces. Injury to the liver often affects biliary function and impairs this route of elimination.

Elimination of chemicals from the body can be studied by pharmacokinetic measurements, which are often based on the remaining concentration of a chemical or its metabolites in the blood in relation to time. Such information usually provides a good estimate of the amount of the chemical available for toxic action. However, storage of the chemical in tissue depots or the toxicity of unmeasured, activated, intermediate chemical forms is sometimes more important.

Processes of metabolism and elimination can be altered in the elderly, but the evidence of altered hepatic drug metabolism in humans is indirect. Autopsy studies have demonstrated that

liver mass in proportion to body weight declines after middle age and that liver blood flow decreases with increasing age. For some drugs, mainly those that undergo conjugation in the liver, there is no clear effect of age on metabolism. However, age appears to have a variable influence on the rates of metabolism of drugs that are oxidized in the liver; most of the wide interindividual variation in drug metabolism is more likely due to a variety of genetic and environmental factors. Although the available data indicate no effect of age on the inhibition of drug metabolism (Divoll et al., 1982; Vestal et al., 1987), the equally limited data on the susceptibility of the elderly to induction of hepatic drug metabolism conflict, some studies showing a decrease in the extent of induction (Salem et al., 1978; Twom-Barina et al., 1984) and others no age differences (Crowley et al., 1986; Pearson and Roberts, 1984). The effect of age on the induction and inhibition of drug metabolism, as well as other drug interactions, requires further investigation.

Cigarette smoke contains polycyclic hydrocarbons, which are potent inducers of some isozymes of cytochrome P-450. Most cross-sectional studies have indicated that cigarette smoking is associated with less induction of biotransformation in elderly than in young people. Whether this is intrinsic to aging or is the result of selective mortality could be established only by longitudinal studies, which have not been done. Nevertheless, the possibility of the greatly reduced capacity of some elderly patients to metabolize and eliminate drugs should be taken into consideration when prescribing drugs for the elderly. This can be done either by slightly reducing the dosage of potent drugs with low therapeutic indexes or by watching the patients very carefully, to ensure therapeutic efficacy of prescribed medications and to detect undesirable drug-related side effects early.

Studies in senescent experimental animals have shown reduced hepatic enzyme activity, with resulting reduced capacity to metabolize drugs and reduced hepatic enzyme induction. Most of the data have been acquired in rats and mice, and the apparent age-related changes might not be universal; species, strain, and sex differences have been important variables in rodent studies. Studies with liver tissue from nonhuman primates have not shown a significant decline in the content of cytochrome P-450 or in the specific activity of NADPH cytochrome c (P-450) reductase (Schmucker and Wang, 1987). Similarly, in vitro studies with human liver tissue (also limited) have shown no effect of age on

microsomal drug-metabolizing activity (Woodhouse et al., 1984). The results conflict with those obtained in rodents, and to some extent they conflict with in vivo studies in humans. (In vivo studies in nonhuman primates have not been performed.) They do emphasize, however, the difficulties in extrapolating observations made in experimental animals to humans and the need for clinical investigation to evaluate the metabolism of drugs and chemicals in humans.

One important chemical that is widely used as a drug by persons of almost all ages is alcohol. Alcohol is distributed into total body water. In both rodents and humans, its volume of distribution decreases with age (Vestal et al., 1977; Wiberg et al., 1971). That decrease results in higher blood concentrations after equivalent doses in the elderly than in the young. Acute alcohol exposure inhibits and chronic exposure induces oxidative drug metabolism in the normal liver. Alcohol itself is oxidized predominantly by alcohol dehydrogenase, a cytoplasmic hepatic enzyme, and to a lesser extent by the hepatic microsomal enzyme system. Although the elderly are more sensitive to the behavioral and cognitive effects of alcohol, studies have not demonstrated age differences in alcohol metabolism in humans (Vestal et al., 1977). Age has been shown to influence alcohol metabolism in rats (Wiberg et al., 1970).

Dietary composition is an important environmental determinant of drug metabolism and drug toxicity (Alvares et al., 1979; Campbell and Hayes, 1974). Most studies have been conducted in experimental animals (Campbell and Hayes, 1974). Studies in healthy human volunteers have shown that a low-carbohydrate, high-protein diet (Kappas et al., 1976) and charcoal-broiled beef (Kappas et al., 1978) increase the metabolism of antipyrine and theophylline, and dietary brussels sprouts and cabbage (Pantuck et al., 1979) increase the metabolism of antipyrine and phenacetin. Charcoal-broiled beef contains benzo [a]pyrene and other polycyclic hydrocarbons (Lijinsky and Shubik, 1964), which stimulate the metabolism of benzo[a]pyrene in rat liver and placenta (Harrison and West, 1971). Brussels sprouts, cabbage, turnips, broccoli, cauliflower, and spinach induce benzo[a]pyrene hydroxylase in the rat (Wattenberg, 1971). Indol compounds in cabbage and brussels sprouts stimulate the metabolism of phenacetin, hexobarbital, and 7-ethoxycoumarin by rat intestine (Loub et al., 1975; Pantuck et al., 1976).

The extent to which the elderly might differ from younger adults in their response to manipulations of carbohydrate, protein, polycyclic hydrocarbons, cruciferous vegetables, and other dietary constituents requires investigation. Some attention has been given to clinical micronutrient-deficiency states. Treatment of ascorbic acid deficiency was associated with an increase in the plasma clearance of antipyrine in elderly patients admitted to a geriatric ward, but there was no difference in basal values between deficient and nondeficient patients, and there was no effect of ascorbic acid treatment in the nondeficient group (Smithard and Langman, 1978). In another study, changes in dietary ascorbic acid did not affect caffeine metabolism in the elderly (Trang et al., 1982). Although poor nutrition and dietary habit might contribute to the complex changes seen in hepatic drug metabolism in old age, the available data are inadequate to substantiate such a conclusion (Cusack and Denham, 1984).

In contrast with hepatic function, diminished renal function is common and easily measured in the elderly. Studies have indicated that both glomerular function and tubular function are affected by aging. Glomerular filtration rate, as measured by inulin or creatinine clearance, can fall by as much as 50%. Renal plasma flow declines by approximately 2% each year. The decline in renal function decreases the rate of elimination of drugs that are excreted unchanged by the kidney. In clinical medicine, reduction in the maintenance doses of drugs, such as the aminoglycoside antibiotics and the cardiac glycoside digoxin, is often necessary to prevent toxicity.

The decline in renal function is quite variable; some people exhibit little or no apparent decline (Lindeman et al., 1985). Therefore, in clinical practice it is essential to measure plasma concentrations of potentially toxic drugs and adjust doses accordingly to achieve therapeutic concentrations.

Not only geriatric patients, but fetuses, neonates, and children show rates of drug elimination that differ from those in normal adults and that can vary greatly with drug and person. For example, antipyrine and phenylbutazone elimination was approximately twice as fast in children 1–8 years old as in normal adults (Alvares et al., 1975). Although eight children without clinical symptoms of acute or chronic lead poisoning, but with biochemical manifestations, had the same rates of antipyrine and phenylbutazone elimination as normal children, two children with both clinical

and biochemical signs exhibited increased plasma antipyrine half-lives. The half-lives returned to the normal range for children when chelation therapy was instituted. Similar results have been obtained in other studies that disclosed more rapid elimination of diazoxide (Pruitt et al., 1973), phenobarbital (Garretson and Dayton, 1970), and clindamycin (Kauffman et al., 1972) in children than in adults.

Human fetuses and neonates have much lower capacity than children or adults to eliminate drugs, although human fetuses and neonates, in contrast with those of some rodents, exhibit measurable hepatic microsomal drug-metabolizing activity (Pelkonen et al., 1973; Rane and Sjoqvist, 1972). In premature infants, the rates of elimination of some drugs appear to be even lower than those in full-term healthy newborns. For example, plasma indomethacin half-lives were 2 and 24 hours in two premature infants (Friedman et al., 1978), whereas the mean value was 4.7 hours in full-term healthy newborns (Traeger et al., 1973) and 2–3 or 7.2 hours in healthy adults (Duggan et al., 1972; Hucker et al., 1966; Palmer et al., 1974). Obviously, the marked differences in elimination rates among premature infants, full-term newborns, children, and adults have practical significance in the calculation of appropriate dosages. They also indicate the need to investigate pharmacokinetic and pharmacodynamic processes for many more drugs with respect to various age groups.

All the characteristics described here are important in studying the effects of environmental chemicals on aging. If the effects of chemicals on aging mimic other human health effects, the members of an exposed human population will not all react in the same way. The wide genetic heterogeneity of the human population will ensure differences in responses to environmental chemicals even among members with comparable exposures.

MECHANISMS OF TOXICITY AT THE MOLECULAR, CELLULAR, AND TISSUE LEVEL

The mechanisms by which toxic agents exert their actions are extremely diverse. Such mechanisms vary between specific agents and between doses of a given agent. Mechanisms of toxic action can be characterized by the dose at which the essential toxic effect is induced and by the specificity of that effect. Such a characterization is probably most relevant for the consideration of

aging, in that the age-associated functional decline in physiologic systems and the lack of specificity as to cells and tissues have been characterized for elderly people, even though the exact mechanism of aging is still unknown.

Molecular Action

The molecular action of toxic agents can result from the creation of damaging chemical species that attack specific moieties of biologic molecules. The search for toxic mechanisms that are shared by aging and by specific toxic agents should include agents whose action is very broad, because aging broadly affects all tissues. Breadth of action can result from different types of mechanisms, however. Equally desirable would be the discovery of agents whose molecular mode of action influenced a specific aspect of the senescent phenotype, inasmuch as this would allow a finer dissection of mechanisms.

Damage can be induced in a specific molecule whose altered function can result in a broad range of toxic action. Damage to DNA with pleiotropic effects is an example. General toxic effects can also take place through agents whose molecular damage is by the production of a general damaging species. For example, ionizing radiation and many chemical agents produce free radicals either directly or by the action of intrinsic metabolic processes. Such free radicals, themselves or through a cascade of processes, can interact with many biomolecules to produce types of damage having different potential for biologic effect.

Furthermore, one tissue can be susceptible at one magnitude of exposure and other tissues at other magnitudes. Using ionizing radiation as an illustration, x rays produce a variety of ions and radicals in irradiated tissue. In exposed humans, high doses of x rays (over 100 Gy) can induce central nervous system collapse within minutes or hours. At lower doses (10 Gy), the dominant toxic effect occurs by inhibiting proliferation of the stem cells of gut crypts; the inhibition denudes the intestinal mucosa and leads to death within days. At still lower doses (1 Gy), x rays not only derange the hematopoietic system, but also increase cancer in irradiated populations. At very low doses (below 1 Gy), x rays produce both excess cancer and heritable mutation; cancer is considered the greater risk. The responses to the lower exposures have been observed in both epidemiologic and animal studies.

As discussed (Lindop and Rotblat, 1961; National Research Council, 1972; Sasaki and Kasuga, 1981), x rays produce life-shortening, as well as the other toxic effects. Thus, they provide an example of an agent that produces a nonspecific toxic free radical, which in turn attacks susceptible biomolecules. The biologic response, however, can be specific to various tissues, the dominant effect depending on the exposure dose.

Another principle of toxicology, that of limiting toxicity, is involved in the preceding example. Animals that succumb to very high doses of x rays would also suffer other toxic effects if not limited by the more severe and immediate effects. In considering the possible effects of any toxic agent on aging and the aged, we must view such an induced response as part of a series of toxic actions and as depending on dose, mode of exposure, duration of exposure, species exposed, and period of observation.

Other toxic agents are probably more specific in their initial actions and in their effects. For example, carbon monoxide binds to hemoglobin, reduces the oxygen-carrying capacity, and produces toxicity.

A final consideration of damage at the molecular level that could result in the pleiotropic manifestations observed in aging is whether a specific toxic action can be manifested in more general ways. It has been proposed that a specific action of a specific tissue can result in multiple deteriorative processes in various tissues. Although alterations in molecules that control regulatory processes can have multiple manifestations or can affect multiple tissues (e.g., in diabetes), no example of induced response equal in breadth to the manifestations of aging has been observed.

Cellular Effects

Toxic mechanisms can act at the level of the cell in two general ways: specific tissue functions can fail if enough cells of a specific type in that tissue are altered by the exposure, and toxic stress of a single cell can produce some toxic effects (as in cancer), heritable mutation, and teratogenesis. Aging must be considered a phenomenon in which most cells in most tissues can be discerned to be altered, so it seems logical to consider aging as similar to the first cellular effect mentioned, that is, as acting through deterioration in most cells of a given tissue.

The results of some aging studies have indicated that the

cell is the essential unit of aging, with manifestations at the tissue, organ, and organism levels being sequelae of cellular deterioration. Although aging research has been directed toward determining the molecular damage or change that underlies cellular aging, it has been unsuccessful in establishing a molecular etiology. Thus, in a search for toxic agents that mimic aging, comparisons at the level of the cell and tissue are appropriate.

Effects at the Tissue Level

Toxic action in intact animals is most often characterized at the tissue level because altered tissue structure or function is commonly observed. Such specificity might be due to toxic stress at the site of exposure (e.g., lung, skin, or gastrointestinal tract), at the site of metabolic action (e.g., liver, brain, or kidney), or in susceptible target cells. It is important, however, in understanding the toxic mechanism acting at the tissue level to determine its etiology at the cellular and molecular levels.

To return to the example of ionizing radiation, the induced failure of the lining of the gut to perform its barrier function is the direct result of failure of stem cells to proliferate, which causes sloughing of the intestinal mucosa. The failure of the stem cells to proliferate is believed to proceed from the action of x-ray-induced free radicals in their chromatin through mitotic inhibition. Thus, when considering toxic effects related mechanistically to aging, the basic goal must be to identify the sequence of events from molecular changes to their sequelae at the level of the cell, the tissue, and the organism.

PHARMACOGENETICS

In the course of investigations of drug metabolism and drug disposition in humans, striking individual differences in response to drugs and in ability to metabolize and dispose of drugs have been noted. Some differences are due to environmental factors, some to age-dependent (developmental) factors, others to genetic factors, and many to complex interactions among those factors. The scientific study of genetic factors that account for individual differences in drug metabolism and drug response is called pharmacogenetics. Pharmacogenetics is of toxicologic importance in

that it reveals how some people, because of their genetic constitutions, suffer toxic effects on exposure to xenobiotics at doses well tolerated by other people.

Of particular interest is the relationship between genetic differences in rates of metabolism among subjects and the synthesis of potentially toxic biotransformation products of a parent drug or other chemical. In the past, the hepatic drug-metabolizing enzyme system has been regarded as a detoxification system, because it converts lipid-soluble compounds that could otherwise remain in the body indefinitely to more polar metabolites that are readily excreted in urine. More recently, however, it has been recognized that this enzyme system can produce potentially toxic, highly reactive metabolites that combine with tissue macromolecules, including DNA, to produce necrosis, immunologic reactivity, and mutations (Sipes and Gandolfi, 1986).

Qualitative differences among subjects in pathways of drug metabolism and quantitative differences in the activities of the enzymes that catalyze those reactions and pathways could be involved in the regulation and control of such tissue damage. Thus, genetic differences among subjects can render some more and others less sensitive to the toxicity of different reactive metabolites.

As genetic entities are investigated in detail, the effects of age on their expression often become apparent. Expression of a phenotype, and hence genetically modified (increased or decreased) susceptibility to chemical agents, might occur only when a person bearing genes that predispose to a particular kind of toxicity is first exposed to the offending environmental chemical, and that might not happen until late in life. Drugs are prescribed more commonly to old than to young people, so the incidence of pharmacogenetically related drug toxicity might be expected to increase with age. In addition, some genetically determined conditions are expressed only relatively late in life, such as Huntington's chorea and some forms of neuromuscular disease and diabetes mellitus.

Many factors have been systematically investigated and identified as contributing to the large interindividual variations that characterize disposition and response to xenobiotics in humans (Figure 4–1). The factors include sex, time of day or season of drug administration, presence of disease, hormonal and nutritional status, stress, exposure to activators or inhibitors of the

hepatic microsomal drug-metabolizing enzymes (including chronic administration of any of several hundred drugs), the status of the heart, liver, kidneys, and endocrine organs—and age (Conney et al., 1971; Gillette, 1971; Vesell, 1982b).

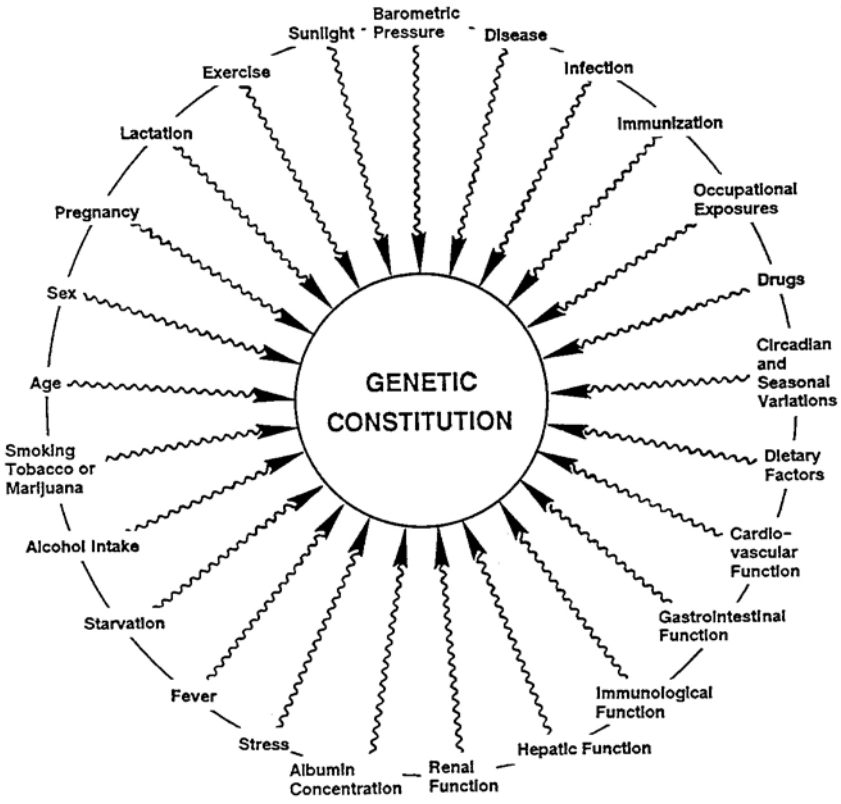

FIGURE 4–1 Schematic depiction of established or suspected environmental factors that can alter genetically controlled rates of drug elimination. Lines from each environmental factor to a central circle are wavy, to suggest that modification of genetically controlled rates can occur at different magnitudes. Such environmental effects need not occur directly at the genetic level. In the outer circle, a line joins environmental factors, to suggest that several are associated and interdependent, rather than independent. Source: Reprinted with permission from Vesell (1982a).

In the past 20 years, genetic factors that directly affect xenobiotic response and disposition in humans have been discovered

(La Du, 1972; Omenn and Gelboin, 1984; Omenn and Motulsky, 1978; Vesell, 1969, 1971, 1973, 1984; Weinshilboum, 1984). Some 60 factors have been identified, and many more probably exist. In some people under some conditions, genetic factors are the major or even sole cause of such interindividual differences. For example, when age, sex, diet, and exposure to environmental chemicals that activate or inhibit the hepatic drug-metabolizing enzyme system remain constant among human subjects, large interindividual variations in response to and disposition of xenobiotics remain. Many of these variations have a genetic basis.

About 20% of patients in teaching hospitals in the United States are there for treatment of adverse drug reactions, and 5– 30% of the patients in these hospitals have at least one such reaction (Cluff et al., 1965). Adverse reactions to drugs occur more frequently and with greater severity in old than in young patients (Hall, 1982). The normal wide disparity in individual patients' responses to drugs is only one cause of adverse reactions, including drug toxicity, but it constitutes an important contribution to this major medical problem.

Table 4–1 lists 10 of the best-known and most intensively investigated pharmacogenetic conditions. In almost every one, a toxic response ensues owing to drug accumulation secondary to a marked reduction in the enzymatic conversion of the parent drug to pharmacologically inactive metabolites. The function of the enzyme is aberrant because of a point mutation in the gene that controls its synthesis. Like most other inborn errors of metabolism, the conditions listed in Table 4–1 are generally transmitted as autosomal recessive traits. Thus, affected subjects inherit a mutant allele from each of two phenotypically normal parents.

Geographic differences exist in the gene frequencies of several pharmacogenetic conditions. Age effects have also been identified for the acetylase polymorphism, but additional studies of other pharmacogenetic entities in Table 4–1 need to be performed with respect to age.

The history of the discovery of an age effect on the gene frequency of the acetylation polymorphism is particularly instructive, because it illustrates how careful the search for such age effects must be. In the original observations of Evans et al. (1960), age was not recognized as an important factor. Later, study of a small number of subjects seemed to confirm that observation (Farah et

al., 1977). But in 1983, Evans re-evaluated his original data and reported an effect of both age and sex on plasma isoniazid concentrations (Iselius and Evans, 1983). In 1984, the proportion of slow acetylators was found to be significantly higher in older people, but no sex distributions were reported (Gachalyi et al., 1984). In 1985, the age effect on the acetylator phenotype was confirmed, but stated to occur only in males (Paulsen and Nilsson, 1985).

TABLE 4–1 Monogenic Metabolic Pharmacogenetic Conditions and Putative Aberrant Enzymes

Condition[a]	Aberrant Enzyme and Normal Location
Acatalasia	Catalase in erythrocytes
Slow inactivation of isoniazid	N-Acetyl transferase in liver
Suxamethonium sensitivity or atypical pseudocholinesterase	Pseudocholinesterase in plasma
Phenytoin toxicity due to deficient parahydroxylation (autosomal dominant)	Mixed-function oxidase in liver that parahydroxylates phenytoin[b]
Bishydroxycoumarin sensitivity (mode of inheritance unknown)	Mixed-function oxidase in liver that hydroxylates bishydroxycoumarin[b]
Acetophenetidin-induced methemoglobinemia	Mixed-function oxidase in liver that de-ethylates acetophenetidin[b]
Polymorphic serum aryl esterase activity	Serum aryl esterase (paraoxonase)
Deficient N-hydroxylation of amobarbital	Mixed-function oxidase in liver that N-hydroxylates amobarbital[b]
Polymorphic hydroxylation of debrisoquine in man	Mixed-function oxidase in liver that 4-hydroxylates debrisoquine
Polymorphic hydroxylation of mephenytoin	Mixed-function oxidase in liver that hydroxylates S-mephenytoin[b]

[a]Autosomal recessive, unless otherwise noted. Reprinted with permission from Vesell (1982a).
[b]Probable but not fully established site of genetic defect.

The increased frequency of the slow-acetylator phenotype with age is of special interest, because the phenotype is also associated with a markedly increased susceptibility to the development of bladder cancer on chronic industrial exposure to arylamines and hydrazines (Cartwright et al., 1982). Another association between susceptibility to cancer and a pharmacogenetic phenotype has been claimed: extensive metabolizers of debrisoquin were stated

to be more common in patients with bronchogenic carcinoma than in age- and sex-matched controls (Ayesh et al., 1984).

One implication of those variations among normal people is that a given dose of a drug administered by a given route can be toxic in one subject, therapeutic in another, and without pharmacologic effect in a third. The existence of these differences presents a formidable challenge to a physician who must individualize therapy (especially for drugs with low therapeutic indexes).

The therapeutic ramifications of large interindividual variations in the disposition of many drugs make it necessary to identify the mechanism responsible. Such identification is beset with difficulties rooted in the extreme genetic and environmental heterogeneity of human beings. In laboratory animals such as rats and mice, however, heterogeneity can be controlled. Each variable can be manipulated independently, the quantitative contribution of each to interindividual variations in drug disposition can be studied, and dose-response curves can be constructed. In the last decade, such studies have revealed many factors that can affect drug disposition. In humans, pharmacogenetic conditions can be categorized into those that affect how the body acts on drugs (pharmacokinetic conditions) and those that affect how drugs act on the body (pharmacodynamic conditions) (Vesell, 1973).

Because most of the monogenetic (simple, single-gene) conditions mentioned above are rare and make only a few drugs toxic, they probably contribute in only a minor way to the major medical problem of adverse drug reactions. However, another development in pharmacogenetics suggests that genetic differences that directly affect xenobiotic disposition play a prominent role in commonly encountered forms of drug toxicity. Large interindividual variations that existed among unrelated people in response to phenylbutazone, bishydroxycoumarin, antipyrine, halothane, ethanol, phenytoin, nortriptyline, or salicylate were absent in pairs of monozygotic twins, but present in most, but not all, pairs of dizygotic twins (Vesell, 1973, in press). The magnitude of interindividual variations in rates of drug elimination among unrelated people was a factor of 30 for nortriptyline, 10 for bishydroxycoumarin, 6 for phenylbutazone and antipyrine, 3 for halothane, and 2 for ethanol.

The existence and operation of many environmental factors— each with a different capability of altering the basal, genetically controlled rate of drug disposition—make it difficult to attribute

portions of the total interindividual variation to specific environmental factors. The task of partitioning the total variation in drug elimination among large heterogeneous populations is further complicated by the close association of such seemingly pure environmental factors as smoking and diet with other environmental factors, as well as with genetic factors.

Many environmental, developmental, nutritional, or endocrine factors can influence the rate at which a person eliminates a drug. In Figure 4–1 such factors are connected because they are often associated with each other in a given subject rather than being independent. In fact, they often interact dynamically to change a subject's characteristic basal rates of drug absorption, distribution, metabolism, excretion, or receptor interaction. Accordingly, the effects of each of these factors on drug response can be complex and can change with time even in the same subject (Vesell, 1980, 1982a,b).

BIOLOGIC MARKERS

A biologic marker is a biochemical, cellular, structural, or functional indicator of an event in a biologic system or sample. Biologic markers in humans, animals, or other biota can serve as measures of exposure to or injury by a xenobiotic by indicating internal or circulating dose, stored body burden, dose at a target tissue, or the early onset of a pathologic effect.

The concept of biologic markers grew out of cancer research that sought to identify the role of exogenous agents or host factors as causes of human cancer. Perera and Weinstein (1982) defined molecular cancer epidemiology as an approach that combined analytic epidemiology and molecular techniques to identify carcinogens in human tissues, cells, or fluids and to measure early morphologic, biochemical, or functional responses to carcinogens. Lower and Kanarek (1982) described molecular epidemiology as the measurement of molecular characteristics related to neoplastic disease.

Since those early papers, several symposia and workshops have been conducted to examine the use of biologic markers in disease prevention. The ultimate goal of marker research is to improve the predictive relationship between exposure, dose, and response. A more thorough understanding of the role of markers will help to prevent disease by more precisely assessing the magnitude of risk,

identifying high-risk groups or individuals, and providing early warning of disease.

The development of cellular and molecular markers extending from exposure to the development of disease should provide a powerful tool for the environmental health sciences. Markers that indicate the presence of internal or biologically effective doses or of incipient disease can be useful in hazard identification, that is, as the qualitative step that causally associates an environmental agent with an adverse effect. Markers can also be used to determine dose-response relationships, particularly at the low doses relevant to most environmental chemicals. A major role of markers is to clarify the extent of human exposure in populations, the extent of individual exposure, and the proportion of high responders or outliers among the human population (Fowle, 1984).

The use of biologic markers hats raised a number of important ethical issues (Ashford, 1986). Among these is the concern that biologic screening could encourage a shift from *environmental* monitoring to *human* monitoring in the workplace. There is concern that detection of a susceptibility marker, for example, could be used to exclude a person from employment, and that focusing on detecting susceptible populations and excluding them from the workplace could replace efforts to remove toxic chemicals from the workplace.

Markers can be distinguished on a continuum of time as markers of susceptibility, exposure, circulating internal dose, biologically effective dose (or dose at receptor site), and potential or actual health impairment.

Markers of *susceptibility* indicate individual or population physiologic differences that affect response to environmental agents, regardless of exposure. They include differences in receptors, in metabolism, in immunoglobulins, or in organ reserve capacity or other variations that lead to altered response to environmental agents, including sex, age, physiologic state, and even diet. For example, the absence of the enzyme α-1-antitrypsin is a marker of susceptibility to chronic obstructive pulmonary disease.

Markers of *exposure* are biologic events or conditions that reveal information about external exposure, internal absorbed dose, or dose at the receptor site or site of toxic action. Markers of *internal dose*—indicating the amount of a material that is absorbed into the organism—include such pharmacokinetic characteristics

as blood flow, capillary permeability, transport mechanisms, number of receptor sites, metabolism of the material, and route of administration. Additional factors include data on structure and stability of the material, peak or cumulative circulating dose, and half-life (Gibaldi and Perrier, 1982). Markers of *biologically effective dose* include such target-organ characteristics as rates of metabolic activation and detoxification, pre-existing susceptibilities, and reserve capacity.

Markers of potential *health impairment* include early biologic responses, such as alterations in the functions of target or nontarget tissue shortly after exposure. Later in the course of response to a toxicant or after accumulation of high doses, markers of health impairment include altered function of the affected tissue that could be considered a preclinical state of disease.

Exposure to environmental pollutants can lead to uptake of a biologically effective dose and ultimately to reversible or irreversible injury. Different types of markers can be used differently to determine exposure, dose, or health impairment. However, markers of these types are not always distinct from each other. Thus, markers of exposures and markers of effects are often difficult to differentiate.

Because the body responds to injury with only a limited number of biochemical or cellular changes, an effect marker might not always be specific for an individual pollutant.

TOXICITY TESTING

Toxicity testing is undertaken for two general purposes: to characterize a particular chemical or physical agent so as to determine its general or specific toxic properties, and to screen a large number of agents for their likelihood of producing particular toxic effects. In both cases, practical and scientific considerations influence decisions about the nature and extent of testing. Each decision entails a scientific judgment that is based both on known toxic mechanisms and on data from tests of many chemicals with a series of defined protocols. Practical restraints on resources and time limit the testing of any particular agent. The complete testing of an agent in the wide range of available standard protocols could cost tens of millions of dollars. Few agents are theoretically or practically important enough to justify such expenditures.

Toxicity-testing protocols can be divided into screening or

auxiliary tests and whole-animal tests. Screening or auxiliary tests are usually short-term tests designed to identify a potential for inducing specific toxic effects. Whole-animal tests can be short term or long term and are designed to confirm or deny potential toxicity and to assay risk quantitatively.

Two characteristics of screening tests determine their utility. The first is whether the biologic process assayed by a test is identical with the process involved in the toxic effect of concern. For instance, is mutation as observed in the *Salmonella typhimurium* test a necessary and sufficient process in some or all types of carcinogenesis for which the test is used as a screen? The answer to this specific question about the Ames assay is probably no; other processes not detectable by this test are also relevant to the induction of cancer. Regardless, the Ames assay is a useful test because it has the second characteristic: predictive value.

Predictive value is the ability of a test to predict the outcome of another test or human response. It is a probabilistic measure of correlation between the outcome of the simple test and the "truth" as defined through whole-animal testing. Predictive value is independent of essential biology. If, however, a short-term test has power both in mimicking essential biology and in predicting whole-animal response, it approaches the ideal.

In designing screening tests from the toxicologic perspective of detecting agents that accelerate aging, the same criteria apply:

- Does the proposed test mimic the essential biology of aging?
- Does the proposed test detect agents that accelerate aging when tested in whole animals?

These questions accent the problems of designing screening tests for agents that accelerate or interact with aging.

Whole-animal experiments, particularly long-term experiments, are most predictive of human response and quantitative risk. The species tested should represent human populations in exhibiting similar toxic responses and in mimicking human absorption, metabolism, and biodistribution of the chemical agent being tested. Although all animals age, a particular species might be inappropriate as a surrogate for human metabolic response to a particular agent. The selection of species for whole-animal, long-term testing related to aging must serve the dual demands of the gerontologist and the toxicologist, and for the toxicologist that

species will change, depending on the specific agent that is to be tested.

Laboratory tests must, for practical reasons, be performed with relatively small numbers of animals. Tests for environmental agents are generally performed at dosages much higher than those to which human populations are exposed. Data from such tests must be extrapolated to predict human responses to dosages experienced in the environment. This extrapolation requires measurement (or at least prediction or assumption) of the shape of the dose-response curve. Toxic effects are often classified according to whether there is a threshold dose (below which no toxic effects will be observed), or whether at low dosages toxic effects will be produced in only a small proportion of exposed animals. This important distinction must also be considered for toxic interactions with aging.

The measurement of dose-response relationships for reduction in life span is difficult. Dose-response curves for life-shortening are complex and not amenable to simple extrapolation to low doses. One test of the hypothesis that radiation exposure induces premature aging would be the demonstration that the onset of all diseases is advanced to the same extent and by a factor related to the degree of the shortening of the life span (National Research Council, 1980b).

Another extrapolation that must be considered is that from the laboratory to the real environment. Laboratory tests have most commonly been performed with protocols wherein a single agent is tested for its toxic effect; however, the human environment contains multiple agents that can interact. In addition, there is little evidence that interaction occurs between agents at the low concentrations often found in the environment, but it is important to consider the possibilities of such interactions. Interactions of multiple agents are now being considered for their toxic effects, and the results might guide similar efforts to study age-related effects.

5

Characteristics of the Environment, Aging, and the Aged

The toxic environments of the aging and the aged are diverse. A person's environment includes at least the following components: water, food, air, x rays, ultraviolet radiation, visible light, heat, life-style, pharmaceuticals, and health maintenance. Food and water can be considered separately, inasmuch as a federally established dichotomy assigns the analysis and regulation of water to the Environmental Protection Agency and the analysis and regulation of food primarily to the Food and Drug Administration. Scientific considerations have followed this dichotomy. Life-style is included as a component of a person's environment because of the profound impact of such phenomena as smoking, recreational sun exposure, and recreational drug use on disease prevalence and longevity.

Pharmaceuticals, even though they play an important role in health maintenance, are considered separately. Health maintenance is a more generic and inclusive category, and changes in health care (with changes in diet) have been documented as the principal cause of extended life expectation in many countries (U.S. NIEHS, 1977, 1984).

Although a person might live in a general environment that seems constant, even over a long period, exposure to potentially toxic agents varies widely, that is, the toxic environment changes.

Chemicals in the air, in food, and in water vary widely, even in isolated environments. Whether these changes are significant with respect to aging or the aged is one of the main questions in this study. In any event, it is both useful and correct to state that there is no average toxic environment. Therefore, no average toxic environment can be simulated in a laboratory, and there is no way to perform laboratory experiments whose results can be extrapolated in a general way to the composite human environment. However, the fact that human populations live in different environments offers an opportunity for comparative studies in biochemical toxicology.

All elements of the human environment contain toxic substances. The important question is whether exposures to these substances affect aging or produce toxic effects. This question can be framed in the context of each constituent of the environment.

- *Water.* The content of drinking water varies widely with locale. Generally, few substances are deliberately added to drinking water; those deliberately added include chlorine species and fluorides. Some chemicals found in trace concentrations in water supplies have been tested for some toxic effects and others have not. For instance, pesticides and other commercial chemicals have been detected in many water supplies, but at concentrations deemed by regulatory agencies to constitute only reasonable hazards to public health. What is not clear is whether the toxicologic methods applied by regulatory agencies can evaluate age-associated toxic effects adequately.
- *Food.* The term food, as opposed to diet, applies to the intake in foodstuffs of possibly toxic substances that can alter life span, as distinct from quantitative intake of putatively nontoxic normal foodstuffs. Food consists mainly of complex mixtures and is not well defined from a toxicologic perspective. The ingestion of food accounts for the bulk of the chemical substances that enter the body, of which most, but not all, are probably innocuous. Food acts both as an inducer of biologic processes relevant to aging and as a carrier of potentially deleterious substances. These substances can be divided grossly into four components: natural constituents, contaminants from the environment of its growth, contaminants from its processing, and contaminants from its preparation.
- *Air and its contaminants.* Inhalation has the third greatest responsibility (after ingestion of food and water) for bringing

chemical substances into contact with the body. Of the airborne agents that produce specific toxic effects, the major one is cigarette smoke. Inhalation can bring both gases and particles into contact with the lining of the airways. These substances differ with respect to absorption and clearance via the mucociliary escalator and possible toxic effects. Breathing volume, clearance, and absorption vary with age. The makeup of air varies greatly among geographic locations and among indoor, outdoor, and occupational environments. The aged generally spend more time indoors and less time in occupational environments than do others. But the variation among indoor environments is so great that it precludes generalization about exposure.

- *Pharmaceutical exposure.* Pharmaceutical agents, as opposed to environmental agents, are designed to elicit biologic effects. The toxicologic data on pharmaceuticals are extensive and usually include substantial human response data. Consideration of the pharmaceutical environment is important to the problem being evaluated in this report for two main reasons. First, the aged are exposed to pharmaceuticals more than the young. Second, some pharmaceutical agents place biologic stress on exposed people. If an essential component of aging is a reduction in the capacity to respond to stress, then consideration of aged people's responses to pharmaceuticals could be important. There is no typical or average pharmaceutical environment for the aged, but some groups with defined pharmaceutical exposure for extended periods might be important in studying the response of aged populations to toxic stress.
- *Life-style.* Life-style—including smoking, sun-tanning, and taking of recreational drugs—is included as a separate category of environmental exposure for two reasons. First, life-style is considered as creating optional environmental exposure. Second, exposures in this category are known or suspected to increase disease prevalence that might shorten life or mimic aging processes, or both. Thus, this category of environmental exposure must be considered avoidable toxic stress that is relevant for only some populations.
- *Health maintenance.* This category is included only because improvement in health care changes life expectancy dramatically in some human populations (Schneider and Reed, 1985).

Improvement in health care is usually accompanied by improvement in nutrition; it has been difficult to separate these two factors as contributors to life-span extension.

NUTRITION

Until fairly recently, there has been a tendency to consider the issue of chemical toxicity and the environment in terms of the contamination of the "natural" environment with man-made pollutants, such as DDT. Efforts like those of Higginson (1969) and Doll and Peto (1981) have led to a growing recognition that the environment includes such factors as diet and life style. Indeed, one of the most important factors in chronic human toxicity is natural components of the diet.

Whereas man-made pollutants (so-called contaminants) are commonly measured in picograms, dietary components that can be toxic are more often measured in milligrams or even grams. Common foods are replete with naturally occurring biologically active compounds, for example, vasoactive amines in bananas, cyanogens in corn, oxalates in spinach, goitrogens in cabbage, and anti-inflammatory compounds in licorice (Sapeika, 1978). This is not surprising, in that the plants forming much of our diet have evolved mechanisms to prevent overpredation by insects (natural insecticides) and other animals (Ames, 1983).

As a whole, it appears (Ames, 1983) that the most important chemical exposure of humans, both in quantity and in diversity, results from diet. Thus, diet is considered to be one of the most important aspects of the environment that should be taken into account in the studies of chemical toxicity and aging. Diet is a broad term that usually includes natural contaminants, such as mold-produced aflatoxin; the residues of food preparation practices, such as mutagens produced by charring of foods (National Research Council, 1982); and food additives. However, in focusing this discussion on nutrition, we will emphasize the portion of diet that maintains an organism's health or growth.

An interesting topic that is excluded from the present discussion is the recently suggested importance of some environmental agents in the induction of parkinsonism, a disease considered characteristic of age. The suggestion was based on the development of a model for parkinsonism related to the production of a metabolite of an agent that causes parkinsonism in humans and animals, and

on the presence of antibodies to this metabolite in people who have parkinsonism but no history of exposure to the chemical (Lewin, 1986).

It is well known that the lack of a nutrient often leads to a deficiency syndrome and that an excess of the same component can sometimes lead to overt toxicity. The current discussion concentrates on manipulations within what is generally considered to be a fairly normal range.

Effects of Nutrition on Toxicity

Various nutritive components have major effects on the expression of toxicity. For instance, by increasing the amount of casein given to rats for a month, one can increase the LD50 (the dose required to kill 50%) of some herbicides by a factor of at least 6 (Shakman, 1974). Protein quality and methionine content might also affect the detoxification of some pesticides (Boyd, 1972). Compared with purified diets, cereal-based chow suppressed diphenylhydantoin-induced cleft palate in mice (McClain and Rohrs, 1985).

Because chronic disease often has a long latency, it can be especially susceptible to the influence of nutrition. Nutrition is important in the pathogenesis of coronary heart disease, gallstones, appendicitis, varicose veins, obesity, hiatus hernia, and cancer (Burkitt, 1982). Some of these relationships have become evident through the effect of a change to Western diet in groups whose traditional diets were different; for example, Eskimos who switched to Western diets suffered an increased rate of acute appendicitis (Sinclair, 1982). Other effects have been revealed by epidemiologic studies, such as the Framingham study, which related cholesterol to risk of coronary heart disease (Kannel et al., 1971).

Experimental studies demonstrating the role of diet in chronic disease have been plentiful since the beginning of modern experimental nutrition; for example, some diets influence the progression of atherosclerotic lesions in rabbits (Anitschkow, 1913) and diet modifies induced tumorigenesis in mice (Watson and Mellanby, 1930).

In view of the long history of such studies, the lack of understanding of the mechanisms by which nutrition influences chronic disease and toxicity is surprising. One reason is the complexity of the diet. As noted above, many substances are consumed in food.

Changes in dietary composition can alter xenobiotic metabolism (Rogers and Newberne, 1971), change intestinal microflora quantitatively and qualitatively (Stasse-Wolthuis, 1981) thereby modifying transport and production of bacterial metabolites, affect bile acids (Reddy et al., 1980), and change glutathione synthetase (Beutler, 1972). With the number of substances in food, many of which are needed for maintenance of function, almost any step in the interaction of agent and organism is likely to be influenced by altering nutrition, which would thus lead to an effect on toxicity.

The effects of individual macronutrients, such as dietary protein and fat, on toxicity, longevity, and associated aging events have been explored by altering the dietary content of the macronutrients being assessed. A major problem with this type of analysis is that such changes in dietary composition might influence the amount of food eaten. Unfortunately, the food intake is often not accurately determined or not taken into account in the interpretation of findings. Because the amount and type of food eaten might profoundly influence both aging processes and toxicity of environmental agents, failure to address this issue reduces the value of a study.

The micronutrients, that is, minerals and vitamins, are difficult to study in the context of toxicity and aging partly because there are so many substances in each class of nutrients. In addition, toxicity data are generally lacking on these compounds and elements. There is also little information on the role of these substances in aging, although considerable study has been aimed at ascertaining the relationship of specific components to age-related pathologic processes (e.g., calcium and vitamin D in relation to osteoporosis and calcium and sodium in relation to hypertension).

Because a given nutrient is probably involved at several stages in the maintenance of body function, it might have different impacts on toxicity. This is especially true for the more complex toxic effects such as cancer. Although several factors in the diet might be involved in the toxicity, evidence that one agent can inhibit or promote the carcinogenic effects of another, depending on the sequence of exposures (e.g., Kitagawa et al., 1984), indicates that the effect of altering nutrient intake on complex toxic end points is difficult to determine.

Nutrition and Cancer

Cancer is actually over 200 different diseases. It occurs in almost all tissues that have the capacity to replicate. A recent review summarized much of the present consensus about the mechanisms of cancer (U.S. Interagency Staff Group on Carcinogens, 1986). Simplistically, cancer can be considered as a multistage process that usually involves agent uptake; agent metabolism (for carcinogen activation); cellular processes, such as DNA repair and proliferation; and organismic responses, such as attack by the immune system. Each of these major factors can be affected by changes in nutrition. A recent review (NRC, 1982) analyzed many of these issues. The following discussion gives some examples of the insights that have been gained on the relationship between nutrition and cancer.

One of the most well-tested effects in modulation of carcinogenicity by nutrition is the inhibition of spontaneous and induced carcinogenesis by restriction of total caloric intake. In practice, this is usually accomplished by allowing ingestion of less food than is eaten by a control population. Many studies have demonstrated the effect of caloric restriction, including that of Tannenbaum (1945), who characterized the effect on benzo[a]pyrene-induced mammary tumors in mice, and Kritchevsky et al. (1984), who found a similar effect in 7,12-dimethylbenz[a]anthracene-induced mammary tumors in rats. Life-span studies have shown a decrease in the incidence of spontaneous tumors of many types. Human evidence is less clear because it is hard to separate the effects of changes in diet composition and total caloric content, socioeconomic status, and so on; but there is some evidence that the incidence of colorectal cancer is affected by caloric intake (e.g., Hill et al., 1979).

Lower dietary protein content is generally associated with lower incidences of tumors (NRC, 1982), such as 3-methylcholanthrene-induced mammary adenocarcinoma in rats fed high-protein diets (Shay et al., 1964) and aflatoxin-induced liver tumors in rats (Newberne and Rogers, in press). In contrast, Clinton et al. (1979) found that a decrease in dietary protein increased the incidence of mammary tumors induced by 7,12-dimethylbenz[a]anthracene and that the protein effect depended on the sequence of nutritional changes and agent administration.

Increased dietary fat has been implicated in an increasing

incidence of cancer at several sites (NRC, 1982). For example, increasing dietary fat from 5% to 20% usually increases the incidence of mammary tumors —both spontaneous tumors and, depending on the carcinogen used, induced tumors. Interpretation of the effect has been complicated by the observations that restricting total calories eliminates much of the high-fat effect (Kritchevsky et al., 1984), that energy intake, and body size play a role (Boissonneault et al., 1986), and that essential fatty acids are also important.

Dietary fiber has been implicated in modulating toxicity. However, there are many different dietary fibers, and they might act by various mechanisms, such as by altering the metabolism of dietary agents (DeBethizy et al., 1983) or altering the turnover of gastrointestinal epithelium (Cassidy et al., 1981).

Most of the recent work on cancer and vitamins has focused on vitamins A, C, and E. As a rule, vitamin A deficiency increases susceptibility to tumors, and an increase in its intake is protective. However, vitamin A also induces tumors in hamsters (Smith et al., 1985), and retinyl acetate, a related compound, increases hormone-induced mammary carcinogenesis in mice (Welsch et al., 1981). Vitamin C has little effect on carcinogenesis except through its inhibition of the intestinal reaction of nitrites with amines to form nitrosamines (Mirvish, 1981).

There are a number of mechanisms by which vitamin E could inhibit cancer formation, particularly by its antioxidizing activity. Most animal studies have tended to confirm this effect, but others have found no such effect, and a few have found that vitamin E enhances carcinogenesis under some conditions (Newberne and Suphakarn, 1983; Toth and Patil, 1983; Wattenberg, 1972).

There has been little systematic evaluation of the effect of minerals on carcinogenesis. Selenium can be carcinogenic (USNCI, 1980); but it also appears to protect against the formation of some induced tumors (Medina et al., 1983; Newberne et al., 1986).

Thus, the role of nutrition in carcinogenesis is far from fully understood. However, two observations are worth noting in regard to the effects of nutrition on aging. One is that the effects of changes in nutrition or carcinogenesis are not simple or even monotonic (i.e., an increasing effect with increasing nutrient content). That is not surprising, inasmuch as the diet is a complex mixture and carcinogenesis is complex. Defining the components of and biologic response to a standard semisynthetic diet, such as

NIH-31, might eliminate some of the problems encountered with the commonly used commercial diets.

The second observation (discussed more extensively in the following sections) is that, of the various nutritional modifications, caloric restriction is likely, at least initially, to be the most generally important for chronic end points. Although caloric restriction is a broad brush that involves many integrative, physiologic, metabolic, and cellular processes, it appears to have the most reproducible effects on chronic end points. Therefore, it is reasonable to assume that it is highly likely to provide a route to the understanding of mechanisms of aging.

Nutrition and Aging

Although the discussion of environmental influences on toxicity and aging has not traditionally considered nutrition explicitly, eating and drinking are the greatest sources of chemical exposure of humans. Diet has an effect on toxic response, both acute and chronic. Nutrition is also known to be a factor in the development of chronic disease in humans and animals. However, the complexity of diet involves many steps in the interaction of agent and organism. The more complicated the interaction, the more complicated the influence of diet. Indications that this is true are the multiphasic responses of agents that interact with carcinogens and that can function as promoters or inhibitors, depending on the timing of exposure. Such complex behavior is manifest when cancer is used to model the interaction of toxicity and nutrition in regard to aging processes.

Background and Criteria for Evaluating Aging

The data from the cancer model on the effect of nutritional modulation in general and caloric restriction in particular constitute only one of many indications of an important role of nutrition in toxicity. In addition, nutrition is often claimed to be important in influencing the aging processes of humans and other animals (Porta, 1980). Some published data do indicate that nutrition modulates many adverse effects of aging (Masoro, 1985). Furthermore, some nutritional regimens and dietary components appear to promote aging processes, or at least the occurrence of age-associated deterioration (Guigoz and Munro, 1985). A substantial

data base exists on nutrition and aging, as well as on the role of nutrition in cancer, but strategies to determine the mechanism by which nutrition modifies these processes are needed.

However, before considering the effect of nutritional modification of aging, we should clarify some of the concepts that underlie research in this field. In tumorigenesis, "bumps and lumps" can be counted fairly directly, but the situation for aging is more complex. Changes in longevity have been widely used as criteria for determining the impact of dietary modification on senescence. However, there are problems with that approach. For instance, during the last 140 years, life expectancy at birth in the United States has markedly increased (Hazzard, 1983). The increase is probably not a result of factors influencing basic aging processes, but rather results primarily from protecting the population from premature death due to specific infectious diseases and injuries.

A change in the life span of a species is a better criterion than life expectancy. A nutritional manipulation that increases life span probably does so by lowering the rate of aging. However, a nutritional manipulation that decreases life span might do so by speeding the aging process or through a number of other possible mechanisms, such as modifying responses to toxic reactions or speeding disease processes.

A major problem in the use of longevity as a criterion to identify factors influencing the rate of aging is the length of time needed to make this assessment. Indeed, for practical purposes this criterion can be used only with short-lived animal models such as rodents. Therefore, there has been much effort toward developing reliable biomarkers of aging (Reff and Schneider, 1982).

It has been difficult to be certain that a particular functional or morphologic measurement is a reliable biomarker of aging, because it is not possible to define aging in the fundamental biologic terms that could serve as a primary standard. Changes in many functional activities and the occurrence of many disease processes are associated with aging, and it is important to learn about nutritional manipulations that influence these age-associated events. However, the influence on such age-associated events should not be taken as evidence that a nutritional manipulation has modulated the aging processes.

Food Restriction

The only nutritional manipulation that has been shown to increase life span in mammals is food restriction, and it has been truly demonstrated only in laboratory rodents. The phenomenon was first demonstrated by McCay and Crowell (1934) and has been confirmed by many others (Barrows and Kokkonen, 1977). Although the dietary protocols have varied widely, all successful approaches have reduced caloric intake by 20–60% (Weindruch, 1985). In the initial studies, food restriction was started at weaning; it was later found that life span also increased when food restriction began during adult life (Beauchene et al., 1986; Cheney et al., 1983; Goodrick et al., 1983; Stuchlikov et al., 1975; Weindruch and Walford, 1982; Yu et al., 1985). Indeed, Yu et al. (1985) found that food restriction begun at the age of 6 months (early in adult life) was as effective in extending the life span of rats as that begun at the age of 6 weeks (2 weeks after weaning).

This effect of food restriction has not been shown in other mammals, but careful research has not been done on long-lived mammals. Findings similar to those in rodents have been obtained in nonmammals: protozoa (Rudzinska, 1952), rotifers (Fanestil and Barrows, 1965), *Daphnia* (Ingle et al., 1937), *Drosophila* (Loeb and Northrop, 1917), and fish (Comfort, 1963).

Food restriction not only influences longevity, but delays or prevents many age-related functional changes (Table 5–1). It also slows or prevents a spectrum of age-associated diseases (Table 5–2).

McCay et al. (1935) suggested that food restriction delayed the aging processes by slowing growth and development. The findings of Barrows and Roeder (1965) supported that view. Indeed, for many years, the view prevailed that retarding maturation and slowing and prolonging growth were at the basis of the effects of food restriction on longevity. However, since 1965, many studies have challenged the concept (Cheney et al., 1983; Goodrick et al., 1983; Stuchlikov et al., 1975; Weindruch and Walford, 1982).

Moreover, Yu et al. (1985) found that food restriction in rats only from the age of 6 weeks to the age of 6 months (the period of rapid growth) was less effective in extending life span and retarding age-associated processes than food restriction begun at either the age of 6 weeks or the age of 6 months. Those findings have redirected views on the action of food restriction away from growth

and development to retardation of aging processes in the mature animal.

TABLE 5–1 Action of Food Restriction on Age-Associated Physiologic Changes

Age-Associated Physiologic Change Delayed or Partially or Completely Prevented by Food Restriction	Species	References
Increase in serum cholesterol	Rat	Liepa et al., 1980; Masoro et al., 1983
Increase in serum triglycerides	Rat	Liepa et al., 1980; Masoro et al., 1983
Increase in serum parathyroid hormone	Rat	Kalu et al., 1984
Increase in serum calcitonin	Rat	Kalu et al., 1983
Loss of response of adipocytes to insulin	Rat	Reaven et al., 1983
Loss of response of adipocytes to glucagon	Rat	Bertrand et al., 1980b; Voss et al., 1982
Loss of response of adipocytes to catecholamines	Rat	Yu et al., 1980
Loss of neurotransmitter receptors and related central nervous system functions	Rat	Joseph et al., 1983; Levin et al., 1981; London et al., 1985
Loss of soluble gamma cystallins from eye lens	Mouse	Leveille et al., 1984
Loss of reproductive function	Rat	Merry and Holehan, 1979; Merry and Holehan, 1985
Loss of skeletal muscle structure and function	Rat	McCarter et al., 1982
Loss of spontaneous locomotor activity	Rat	Yu et al., 1985
Loss of immune function	Mouse	Cheney et al., 1983; Fernandes et al., 1978; Weindruch et al., 1983

Berg and Simms (1960) first proposed that food restriction could increase longevity by reducing body fat. Bertrand et al. (1980a) showed that food restriction decreased not only body fat but also the number of adipocytes in the fat depots. However, the group of rats fed ad libitum showed no correlation between body fat and length of life. Moreover, within the group of food-restricted rats, length of life was significantly and positively correlated with body fat. Thus, the lower fat mass of food-restricted rats does not appear to be involved in the life-prolonging action. On the basis of data from a study in which the duration of food restriction and the part of the life span involved were varied, Stuchlikov et al. (1975) reached the same conclusion. And Harrison et al. (1984), who found that food-restricted obese (ob/ob) mice were fatter but

lived longer than lean littermates fed ad libitum, concluded that reducing body fat does not play a major role in the action of food restriction on longevity.

TABLE 5–2 Action of Food Restriction on Age-Associated Disease Processes

Disease Process Retarded Totally or Partially by Food Restriction	Species	References
Chronic nephropathy	Rat	Berg and Simms, 1960; Bras and Ross, 1964; Nolen, 1972; Saxton and Kimball, 1941; Tucker et al., 1976; Yu et al., 1982; Maeda et al., 1985
Cardiomyopathy	Rat	Maeda et al., 1985
Gastric ulcers	Rat	Maeda et al., 1985
Osteodystrophy	Rat	Maeda et al., 1985
Metastatic calcification	Rat	Maeda et al., 1985
Neoplastic disease	Rat, mouse	Maeda et al., 1985; Saxton and Kimball, 1941; Tannenbaum, 1945; Ross and Bras, 1965; Silberberg and Silberberg, 1955; Cheney et al., 1983; Pollard et al., 1984
Autoimmune renal disease	Mice	Fernandes et al., 1978;
Hypertension-related problems	Rat	Lloyd, 1984

The proposal by Sacher (1977) that food restriction reduces the metabolic rate and by so doing retards the aging processes has been widely embraced. Indeed, Harman (1981) linked the hypothesis to the free-radical theory of aging: if the rate of electron transport and thus oxygen use are reduced, the rate of generation of oxygen free radicals is reduced. Indeed, if these free radicals are important contributors to the aging process, then reducing their production should slow the aging process.

Sacher based his proposal on published data and concepts. Early in this century, Rubner (1908a,b) proposed, on the basis of his studies with domestic animals of various sizes, that all species use a similar number of calories per unit of body mass per lifetime. Pearl (1928) generalized that line of thought and proposed that the higher the metabolic rate per unit of body mass, the higher the rate of aging and the shorter the life. Moreover, there is evidence that limiting food intake reduces the metabolic

rate per unit metabolic mass (Apfelbaum, 1978; Forsum et al., 1981); however, these studies were of short duration (weeks in the case of rats and months in humans). Sacher supported his hypothesis directly with calculations based on published data of Ross (1969) that showed that food-restricted rats consumed the same number of calories per gram of body mass per lifetime as rats fed ad libitum.

Recently, McCarter et al. (1985) directly measured the metabolic rate of rats fed ad libitum and of rats undergoing prolonged, life-extending food restriction. They found that food restriction that markedly increased life span and retarded a spectrum of aging processes did not decrease metabolic rate per unit of lean body mass or "metabolic mass." Thus, the hypothesis that food restriction slows the aging processes by lowering the metabolic rate should be discarded, because its effects on aging can occur without a decrease in metabolic rate.

Masoro et al. (1982) challenged the classical view that food restriction acts by reducing the intake of calories or other nutrients per unit of metabolic mass. They found that lean body mass of food-restricted rats was decreased in proportion to the decrease in caloric intake; nutrient or caloric input per unit of lean body mass or metabolic mass did not decrease.

Thus, food restriction cannot be linked to aging processes by a reduced input of calories or any other nutrient per unit of tissue mass. Rather, the total organism's response to food restriction must be involved. The most likely possibility is that food restriction influences the regulatory systems—endocrine, neural, or both—and that food restriction is linked to aging processes in tissues and organs through these regulatory systems. The nature of the specific regulatory systems involved remains to be defined.

One possibility was suggested more than a decade ago by Everitt (1973), who proposed that food restriction decreases the secretion of an aging factor by the pituitary gland. He and his co-workers found that removing the pituitary (hypophysectomy) of rats (given cortisone replacement therapy only), like food restriction, increased life expectancy, increased life span, inhibited the onset of renal and neoplastic disease, and retarded the aging of collagen (Everitt et al., 1980). The hypothesis was further developed by the following model (Everitt, 1982): food restriction alters

neurotransmitter metabolism within the hypothalamus, which decreases the secretion of a hypothalamic releasing hormone and thus results in decreased secretion of a pituitary hormone.

Although the hypothesis is intriguing, it is not yet supported by a solid data base. Hypophysectomy inhibits food consumption, and that makes it difficult to know the extent to which the findings on aging are due to a direct endocrine influence on aging or are secondary to the decrease in food intake. If they are due directly to an endocrine factor, the nature of the hormone system remains to be defined.

The hypothalamic-pituitary-adrenocortical system is a candidate. The view that hyperadrenocorticism promotes the aging processes hats a long history. Finch and Landfield (1985) reviewed the evidence on which this belief is based. A recent provocative idea is the glucocorticoid-cascade hypothesis of aging proposed by Sapolsky et al. (1986b), which was discussed in Chapter 3.

Food restriction might influence aging by affecting the control systems that regulate plasma glucose concentrations and glucose homeostasis. Cerami (1985) proposed that glucose is a mediator of aging. The hypothesis was discussed in Chapter 3 and should be explored in regard to the mechanism of action of food restriction.

Food restriction markedly retards the aging processes in rodents. It does not do so by reducing the input of a nutrient per unit of body weight. It probably acts via neural, endocrine, or neuroendocrine control systems. Almost no work has been done on the nature of the control systems involved. Although food restriction probably does not act directly on most tissues and organs, it must influence their function via endocrine and neural signals in such a way as to retard the aging processes; the nature of the functional modification is not known.

Support is accumulating for Lindell's (1982) view that food restriction acts by maintaining gene expression. He postulated that enhanced gene expression plays an important role in maintaining cellular homeostasis. Richardson and Cheung (1982) expanded that view by stressing the importance of maintaining protein turnover for adequate cellular homeostasis. Richardson's group (Birchenall-Sparks et al., 1985; Ricketts et al., 1985) has provided evidence that food restriction retards the age-related decrease in the rate of protein synthesis. Lewis et al. (1985) showed that food restriction increased the turnover of body proteins during most of the life span. Surprisingly, the results of the work (Merry and

Holehan, 1985) on the RNA:DNA ratio and the protein:RNA ratio did not seem consistent with the turnover findings.

Unlike the situation with restriction of all food elements or all macronutrients, there is no conclusive evidence that increasing or decreasing the intake of individual specific nutrients (without changing caloric intake) influences the aging processes. This finding might be due not to the absence of such actions, but rather to the inadequacy of the research to date. Research in this field has been both scant and usually flawed. The major flaws have been that the effect of the dietary manipulation under study on life span was not determined and that the influence of dietary manipulation on total food and total caloric intake was not adequately assessed.

Dietary Protein Intake

Results of some studies (Goodrick, 1978; Leto et al., 1976) have indicated that decreasing the intake of dietary protein increases longevity. Results of other studies (Nakagawa and Masana, 1971; Ross and Bras, 1973) have not supported that view. The discrepancy might be related to a failure to measure food intake carefully or to report measurements fully. Davis et al. (1983) studied food-restricted rats that were given diets with varied protein content and concluded that decreasing the dietary protein content decreased longevity. But Yu et al. (1985) found that decreasing the casein content of the diet of male Fischer 344 rats fed ad libitum from 21% to 12.6% caused a small but significant increase in both life expectancy and life span. Caloric intake was the same in both groups of rats fed ad libitum.

The rats on the protein-restricted diet had less severe chronic nephropathy than rats fed the 21% protein diet (Maeda et al., 1985), and that is probably why the rats fed the 12.6% protein diet had increased longevity. The rats with the lower protein intake also had less severe cardiomyopathy and a lower incidence of calcification and degeneration of the skeletal muscle; but incidence of neoplastic disease was not influenced. Replacing the casein in the diet with soy protein, without reducing dietary protein content or changing caloric intake, also increased life expectancy and life span of male Fischer 344 rats (Iwasaki et al., 1986). The major reason for the increase in longevity was thought to be retardation in the age-related progression in severity of chronic nephropathy.

It has been found that tryptophan-deficient diets increase

longevity in rats (Segall, 1979). But they also reduce food intake, and that reduction rather than the tryptophan deficiency itself might be responsible for the increase in longevity.

Dietary Fat Intake

Early studies showed that increasing dietary fat content decreased the life span (French et al., 1953; Silberberg and Silberberg, 1955). High fat contents have also been found to result in the appearance of tumors at earlier ages and to increase the incidence of some kinds of tumors (Carroll, 1975; Clayson, 1975; Reddy et al., 1976). Diets high in fat also accelerate the aging of collagen (Everitt et al., 1981; Hruza and Chvapil, 1962), decrease cell-mediated immunity, and promote autoimmune disease in NZB mice (Fernandes et al., 1972, 1973). The issue not fully addressed in these studies is the extent to which the findings were due to fat itself, rather than to a change in caloric intake.

Dietary Carbohydrate Intake

Little research has been done on the effects of dietary carbohydrates on aging processes. Durand et al. (1968) fed male rats diets containing carbohydrate at 39%; sucrose, glucose, or corn starch was the source of carbohydrate. The life expectancy of Wistar rats was not influenced by the source of carbohydrate, but the life expectancy of BHE rats was reduced when sucrose was the source. Life span was not reported.

Dalderup and Visser (1969) reported that adding sucrose to a complete diet reduced life expectancy of male Wistar rats. They also found that the development of chronic nephropathy was accelerated in the sucrose-fed rats. Data on life span were not reported.

Recent studies by Shafrir and Adler (1984) showed that a diet containing sucrose reduces the length of life, in comparison with the same diet in which starch replaces sucrose. The spiny mouse was the animal model.

The results of studies on the effects of sucrose are provocative. However, none generated detailed survival curves. The effects of sucrose in particular and carbohydrates in general on aging processes deserve further study.

Dietary Vitamin Intake

Kokkonen and Barrows (1985) reported the results of a study in which male C57BL/6J mice were fed ad libitum diets that contained either the amount of vitamins recommended by the National Research Council, half the amount, or 4 times the amount. Life expectancy was significantly reduced when the dietary vitamin content was half that recommended, but not affected by the increase in dietary vitamin content. The interpretation of those results is difficult because food intake might not have been constant, and deficiency or malnutrition might have been the fundamental problem. The complexity of the issue is emphasized by the report of Kayser et al. (1972) that the life span of rats is lengthened by vitamin restriction.

Porta et al. (1980) reported that high dietary vitamin E prolonged the life of rats fed diets that were high in unsaturated fat, but the finding is difficult to interpret because food intake was decreased in rats so treated. Antioxidants, including vitamins, have often been found to increase life expectancy, but not life span, in rodents (Harman, 1978). Moreover, the role of food intake in increasing life expectancy has usually not been adequately addressed.

Dietary Mineral Intake

The effects of reducing mineral intake to the same extent as in life-prolonging food restriction have been investigated in male Fischer 344 rats. The results can be briefly summarized as follows. Restriction of mineral intake did not influence life expectancy or life span. The restriction of sodium, chloride, calcium, and phosphorus to the same extent (40%) that they are restricted in a life-prolonging, food-restriction regimen did not influence life expectancy or life span of male Fischer 344 rats (Yu et al., 1982, 1985).

A marked reduction in the zinc intake of NZB and NZB/W mice, which normally die from autoimmune disease, retarded the development of autoimmune disease and increased longevity (Beach et al., 1981, 1982). However, the increased longevity probably resulted from control of the disease and not from control of the aging processes. The relevance of these findings to the aging of most mice strains and other animals seems doubtful, but they

do point to a need to explore each mineral element in more than one animal model in relation to aging processes.

Special Dietary Requirements of the Aged

Are the nutritional requirements of the American elderly met by the diets they consume? To answer this question, it is necessary to have a reference, or standard, that defines the nutritional needs of the elderly. The commonly used reference in the United States is the *Recommended Dietary Allowances* published periodically by the Committee on Dietary Allowances of the National Research Council's Food and Nutrition Board. The most recent revision was published in 1980 (National Research Council, 1980a). Unfortunately, there is a lack of data on the dietary needs of the elderly. Although seven age ranges from birth to 22 years are considered, only two include people over 22—specifically, 23–50 years and 50 and older. That people 50–60 years old have the same dietary requirements as those over 70 is questionable. The question is recognized in the recommended dietary allowances (RDAs) only for energy allowance, which is lower for people 76 and older.

In addition to the lack of an adequate reference, many methodologic problems and errors have occurred in the study of nutritional requirements and status of the elderly (Garry and Hunt, 1986). They include the use of unstandardized methods, errors in the estimation of nutrient consumption, errors in the analytic values published in food tables, and errors in assumptions about the bioavailability of nutrients in food sources.

To circumvent these many pitfalls, at least in part, nutritional surveillance of the elderly should include assessment of nutrient concentrations in tissues, especially plasma and blood cells. Such analyses present other interpretational problems, of which the primary one is that the relation of tissue concentrations of nutrients to functional impairment has not been well established, particularly if age is a factor in the consideration.

A further problem in regard to the aged is that many have diseases that can influence nutritional needs and status (Flynn, 1984). Although clinicians must deal with all aspects of nutritional requirements of aged patients, including those related to disease, the logical development of our understanding of the nutritional requirements of the aged must first focus on age alone

(i.e., age in the absence of disease). Similarly, many of the elderly might not receive appropriate nutrients because of economic circumstances. Although knowledge of this problem is necessary to permit corrective action, it should not be confused with the nutritional status of the healthy elderly who are not constrained by economic factors, that is, it should not be confused with the basic biologic issue.

What information do we have on the nutritional requirements and needs of elderly people who are free of disease and have adequate economic resources? Garry et al. (1982a) addressed this issue. The subjects were 138 men and 166 women over 60 years old, citizens of Albuquerque, New Mexico, free of major illnesses, and receiving no prescription medication. Most of the subjects were at the middle income level. With the possible exception of a few nutrients, the dietary intake of most subjects appeared to be adequate. Intakes of vitamins B_6, B_{12}, D, and E, folic acid, calcium, and zinc might have been inadequate, inasmuch as one-fourth of the subjects received less than 75% of the RDAs. Indeed, one-fourth of the subjects had vitamins B_6, D, and E and folic acid intakes of less than 50% of the RDAs; in the case of women, that was also true of zinc.

Although the intake of those substances was less than desirable, there is no evidence that the subjects suffered deficiency problems. For example, in the case of vitamin B_{12} and folic acid, none of the subjects had megaloblastic anemia. The low intake of vitamin B_6 and folate might not be real, in that for many foods reliable data on content are lacking. Clearly, much more extensive functional testing is required before intakes can be assessed relative to RDAs with respect to the existence of nutritional adequacy. Not only was the protein intake of most subjects greater than the RDA, but 70% of the protein intake was from animal sources. The influence of protein from different sources, such as vegetables, is not known. Calcium and vitamin D intakes were below the RDAs for most women; they were related to the low consumption of dairy products.

The next step was to learn whether dietary intake, which for the most part seemed adequate, resulted in good nutritional status in the elderly subjects. In regard to vitamin C (Garry et al., 1982c), 95.9% of the population had a plasma ascorbic acid concentration of over 0.4% mg/dl and thus were felt to be at low risk of developing clinical symptoms of hypovitaminosis C. However,

2.2% of the subjects had concentrations of 0.2–0.4 mg/dl and thus were at moderate risk, and 1.9% had concentrations less than 0.2 mg/dl and were at high risk. With an erythrocyte glutathione reductase activity coefficient of over 1.35 as an index of high risk of developing clinical symptoms of hypovitaminosis B_2, only 1% of the subjects were at risk (Garry et al., 1982b). To consider the vitamin D status of the subjects further, plasma 25-hydroxyvitamin D concentration was measured, as was plasma alkaline phosphatase activity, the latter as an index of bone loss (Omdahl et al., 1982). The mean plasma 25-hydroxyvitamin D concentration of the elderly subjects was 15.5 ng/ml, compared with 29.1 ng/ml in a younger control population. Within the elderly subjects, plasma 25-hydroxyvitamin D concentration showed a nadir in January and a zenith in September and was higher in men than women. Plasma alkaline phosphatase activity was inversely related to the plasma 25-hydroxyvitamin D concentration, which might mean that the elderly need moderate vitamin D supplementation and more sunlight.

Further information of this type is needed to define more fully the nutritional status of these subjects and of other populations of healthy elderly people, with regard to the spectrum of nutrients. In particular, more clinical work should be carried out on such people to determine if there are signs of nutritional deficiencies.

The effects of disease must ultimately be considered because there is a high prevalence of disease in the elderly. Indeed, disease in the elderly might result from or be the cause of malnutrition. An obvious example is the extent to which dental problems can limit food choices and eating practices. Thus, the major disease problems encountered in the aged should be assessed with regard to their nutritional aspects.

Osteoporosis is common in the elderly, particularly in women. A number of factors appear to contribute to this problem, and dietary calcium intake could be one (Heany et al., 1982). It has been suggested that postmenopausal women should have a calcium intake of about twice the RDA to prevent loss of bone mass. In fact, however, the calcium intake of most women over 44 appears to be only about 60% of the RDA. Vitamin D intake appears to be well below the RDA; but it should be noted that the efficacy of dietary calcium in retarding osteoporosis is complex and in debate (Riggs and Melton, 1986). The role of the environment in

bone metabolism and Vitamin D nutrition is discussed further in Chapter 7.

A major problem that appears in many at advanced ages is a decline in cognitive ability. There is suggestive evidence that at least in some people this might be related to inadequate vitamin nutrition (Goodwin et al., 1983). However, much more work is needed to define the relationship between cognitive loss and nutrition and to determine the possible therapeutic use of nutrition.

The immune system, including immune responsiveness and autoimmunity, deteriorates with age. These changes could be involved in many aspects of disease in the elderly (Hausman and Weksler, 1985). In rodents, nutrition has been shown to modulate age-related changes in the immune system (Masoro, 1985). No data show clearly that nutrition has such an action in humans, but it is a subject with great potential for the development of beneficial intervention for the aged, and it should be a major research focus of the future.

There is evidence that the pathogenesis of age-related involutional changes of the kidney can be modulated by diet (Brenner et al., 1982). High dietary protein accelerates progression of the lesions, and low-protein diets retard the process.

Atherosclerosis is an age-related disease that has been studied extensively with regard to the role of nutrition (Bierman, 1985)—a role that is still the subject of debate.

Hypertension is an age-related problem that appears in part to be associated with nutrition. The most obvious association is with obesity, which is a risk factor in the development of hypertension. Weight reduction can lower arterial blood pressure in some hypertensive patients (Kannel, 1985). Excessive sodium intake has long been linked to hypertension, but recent evidence has indicated that the extent of its role might have been overgeneralized, inasmuch as only some hypertensive patients respond to changes in dietary sodium intake (Laragh and Pecker, 1983). Recent findings have suggested that inadequate calcium intake might result in hypertension (McCarron, 1985); although controversial, this association might be particularly important in relation to the aged because many have low dietary calcium intake.

Adult-onset diabetes occurs increasingly with advancing age (Silverberg, 1984). Obesity appears to play a role in its pathogenesis, and weight reduction often helps to control it.

Although cancer occurs in people of all ages, the incidence of

many types of cancer (e.g., cancer of the colon) is age-related (Upton, 1977). There is some evidence that diets can prevent or delay the occurrence of cancer, but many more data are needed before firm conclusions can be drawn (NRC, 1982). Cancer often causes malnutrition. Prevention of or treatment of this malnutrition can improve the quality of life of the cancer patient (Flynn, 1984).

The elderly consume many more drugs than the young (Vestal and Dawson, 1985). Drugs affect nutrition by influencing dietary intake, metabolism, and rates of elimination of nutrients (Roe, 1985). In addition, the nutritional status of an elderly person can influence both the efficacy and the toxicity of drugs (Welling, 1985). Thus, there should be increased consideration of drug-nutrient interactions by both medical practitioners and researchers.

Many healthy old people with sufficient income have an adequate intake of most nutrients. However, major exceptions appear to be calcium and vitamin D (see Chapter 6 for further discussion). Lack of sufficient economic resources might well result in malnutrition in the elderly, but that would be true of any age group. An added problem with the aged is the high prevalence of a variety of diseases, many of which can be caused in part or influenced by nutrition and can also adversely affect nutritional status. The aged with such diseases need nutritional programs designed specifically for their particular disease processes.

Many claims have been made about diets and dietary regimens in regard to life extension (Schneider and Reed, 1985). A recent version (Walford, 1986) was based on the food-restriction data base for rodents coupled with an abundant intake of essential nutrients and other substances having some evidence of antiaging action. It should be underscored, however, that there is very little evidence that such diets influence the aging processes of humans. Moreover, there is no evidence that their long-term use will not adversely affect the health of humans.

PHARMACEUTICALS

Demographic Considerations

The proportions of elderly people in developed countries have been rising steadily over the last several decades because of falling birth rates and medical, economic, and social factors that favor

prolonged life. People over 65 years old make up 12% of the American population (more than 23 million people) and spend 20–25% of the national total for drugs and drug sundries, or about $3 billion per year. It is projected that by the year 2030 that age group will contain more than 64 million people and will constitute 21% or more of the population. Thus, by the year 2030 expenditures for drugs by the elderly in the United States might constitute 35–45% of the national total (Vestal, 1985). In the United Kingdom, where the elderly make up 12% of the population, they are already responsible for approximately 30% of expenditures for drug prescriptions (O'Malley et al., 1980). Clearly, the needs of geriatric patients will constitute an increasingly important aspect of medical care in the future.

Patterns of Drug Use and Drug Prescribing

Epidemiologic data are difficult to compare, not only within the United States, but also within and between other countries. The Nordic countries have used the "defined daily dose" (DDD) to lessen the difficulty of comparison (Bergman et al., 1980). This method might be used in future studies in other countries as well. Nevertheless, as reviewed by Nolan and O'Malley (1987a), elderly patients receive more drugs than younger patients.

Ambulatory Populations

In a study of an ambulatory community-dwelling population in Albany, New York, Chien et al. (1978) found that the most commonly used medications were analgesics (used by 67% of the population), cardiovascular preparations (34%), laxatives (31%), vitamins (29%), antacids (26%), and antianxiety agents (22%). Of the 244 persons over 60 who were studied, 83% were taking two or more medications. Over-the-counter (OTC) preparations accounted for 40% of the drug purchases; 60% were prescribed.

In a similar study in Washington, D.C., Guttmann (1978) found that the most frequently used classes of medications were cardiovascular preparations (used by 61%), sedatives and tranquilizers (17%), antiarthritis preparations (12%), and gastrointestinal preparations (11%). OTC drugs were used by 59% of this sample of 447 subjects, 52% using analgesics. Vitamins and laxatives were used by 8% and 7%, respectively, of this group.

A recent study in Seattle confirmed the extensive use of drugs by the elderly. Interviews of 183 independently living elderly residents of two urban high-rise apartment buildings revealed that 75% used at least one prescription drug regularly and 82% used at least one nonprescription drug regularly (Ostrum et al., 1985).

Studies in the United Kingdom have also shown greater drug use in the ambulatory elderly than in the young (Murdoch, 1980; Skegg et al., 1977). The proportion of elderly in a general practice setting taking at least one prescription drug has ranged from 33% in studies of patients over 65 to 80% of males and 85% of females over 75 (Freer, 1985a; Murdoch, 1980). Most studies have indicated that 50–75% of the elderly take at least one prescribed drug (Freer, 1985b; Murdoch, 1980; Shaw and Opit, 1976; Skegg et al., 1977; Tulloch, 1981). Reports from New Zealand (Campbell et al., 1983), Canada (Skoll et al., 1979), Sweden (Boethius, 1977), and Spain (Mas et al., 1983) have contained data that confirm that drug use among the elderly is similar in many other developed countries.

Because of the use of OTC preparations on an as-needed basis, different ways of classifying drugs, and different kinds of patient selection, the data are difficult to compare. However, nonnarcotic analgesics appear to be the most commonly consumed nonprescribed drugs, and cardiovascular preparations and psychoactive substances the most commonly prescribed drugs. Older patients are probably not more avid consumers of OTC drugs, however, than other segments of the population (Bush and Rabin, 1976).

Hospital Populations

It is not surprising that older hospitalized patients receive more drugs than younger ones. That has been documented by studies in the United States (Borda et al., 1967), the United Kingdom (Houston, 1979), and Finland (Sotaniemi and Palva, 1972). However, it is a little surprising how different prescribing practices in different countries can be. A study by the Boston Collaborative Drug Surveillance Program showed that American hospital inpatients received an average of 9.1 different preparations, compared with 7.1 for patients in Canada, 6.3 for Israel, 6.8 for New Zealand, and 4.6 for Scotland.

A detailed comparison between Scotland and the United States showed that patients in the United States were treated

more intensively for diarrhea, dehydration, constipation, diabetes, and hypertension. Anxiety, pain, congestive heart failure, and anemia were treated similarly in the two countries. Differences in prescription patterns were especially obvious in the treatment of infections. Three antibiotics in Scotland and 10 in the United States were used to treat 75% of infections (Lawson and Jick, 1976). Specific data on age were not included in the study, but it seems likely that the findings would apply to geriatric patients.

Why prescribing habits vary so widely among countries, and even among regions of the same country, is not fully understood. The explanation undoubtedly lies in the approach to drug therapy taught in undergraduate and postgraduate medical institutions.

Long-Term-Care Facilities

Patients in chronic-care institutions commonly receive many drugs, tranquilizers and hypnotic-sedatives being very common (Institute of Medicine and National Research Council, 1985). Once again, the comparison between the United States and the United Kingdom is interesting. Estimates of drug use by English nursing home residents are similar to those for elderly patients living in the community and range from 1.5 to 3.1 drugs per patient (Bruce, 1982; Clarke et al., 1981). In contrast, an average of seven drugs are prescribed concurrently for American patients (Bergman et al., 1980; Rawlings and Frisk, 1975; Segal et al., 1979). In both the United Kingdom and the United States, most institutionalized patients over 65 take at least one prescribed drug.

Patients in a long-term-care facility in Boston received a mean of eight drugs in the first 10 days (Borda et al., 1967). In another survey (Kalchthaler et al., 1977), psychotropic drugs were most commonly prescribed (61% of patients), followed by diuretic and antihypertensive drugs (46%), antimicrobials (14%), and cardiotonics (14%). The contribution of consultant pharmacists to rational drug use in long-term-care facilities has been emphasized by Cooper and Bagwell (1978), who showed that over a period of a year the use of scheduled drugs was reduced by 19.4% and the average number of drugs per patient was reduced from 7.2 to 4.8.

Psychoactive drugs might be prescribed more often to patients who are mentally normal and have minimal physical disabilities than to those who are more severely disabled (Ingman et al., 1975). In a study whose results suggested misuse of antipsychotic drugs

in nursing homes, each resident was matched with an ambulatory person enrolled in Medicaid (Ray et al., 1980). Among nursing-home patients, central nervous system (CNS) drugs were the most often prescribed medications, being given to 74% of patients; only 36% of the ambulatory comparison group received CNS drugs.

Nursing-home patients often received prescriptions from multiple categories of CNS drugs: 34% from two or more categories, 9% from three or more, and 1.6% from four. The most common combinations were those of an antipsychotic and a sedative-hypnotic, most often thioridazine and flurazepam. The next most common combinations were those of a minor tranquilizer and a sedative-hypnotic, usually diazepam and chloral hydrate.

The three most commonly prescribed antipsychotic drugs were thioridazine, chlorpromazine, and haloperidol. The authors suggested that those drugs might be used to mold patients into the institutional routine.

Medication Compliance in the Elderly

Many patients have difficulty in taking medications as prescribed by their physicians. Blackwell (1972) reviewed over 50 studies and found that 25–50% of all outpatients completely failed to take their medication.

On the basis of careful review of drug histories in 178 chronically ill ambulatory patients aged 60 or over in the General Medical Clinic at New York Hospital, Schwartz et al. (1962) found that 59% made one or more medication errors and 26% made potentially serious errors. Error-prone patients were more likely to make multiple than single mistakes. The average number of errors was 2.6 per error-making patient. Omission of medication was the most frequent error, followed by lack of knowledge about medications, use of medications not prescribed by a physician, and errors in dosage, sequence, or timing. Almost identical data were obtained using similar techniques in a Seattle-area clinic (Neely and Patrick, 1968).

In a study of geriatric patients 10 days after hospitalization, Parkin et al. (1976) found that 66 of 130 patients deviated from the drug regimens prescribed at discharge. Noncomprehension or lack of a clear understanding of a regimen (in 46 patients) was actually a greater problem than noncompliance or failure to follow instruction (in 20 patients).

Although medication errors seem to be prevalent among elderly patients, studies that used objective measures of compliance have indicated that the elderly are not necessarily more prone to noncompliance than younger patients. That has been demonstrated in patients taking digoxin (Weintraub et al., 1973).

A recent example is the feasibility study for the multicenter clinical trials in the United States called the Systolic Hypertension in the Elderly Program (SHEP), which was conducted between 1980 and 1984. A final cohort of 551 persons over 65 years old with isolated systolic hypertension was enrolled. Compliance with therapy was evaluated by self-reporting, pill counts, and urinary assay for the presence of study drugs. More than 80% of participants in both treatment and placebo groups complied with their SHEP prescriptions (Smith et al., 1985).

Researchers must also allow for intelligent noncompliance by patients who appropriately alter their drug regimen to minimize side effects or to eliminate unnecessary treatment (Weintraub, 1984). Additional research is needed to clarify the clinical importance of such noncompliance in older patients.

Adverse Drug Reactions

Adverse drug reactions might be the inevitable price of improved drug therapy for disease (Barr, 1955; Jick, 1974). The possibility that these reactions are costly in terms of human illness and economics (Campbell et al., 1977; Melmon, 1971) is a matter of controversy. It has been stated that adverse drug reactions constitute a formidable health problem with staggering economic consequences—that one-seventh of all hospital days are devoted to the care of drug toxicity, at an estimated yearly cost of $3 billion (Melmon, 1971).

In support of that contention, previously cited studies from several countries indicate that 3–5% of all hospital admissions are primarily for a drug reaction; that 18–30% of all hospitalized patients have an adverse drug reaction, doubling the duration of hospitalization; and that 30% of these patients have a second reaction during their hospital stay. The lay press has asserted that 30,000 Americans die as a direct result of the use of drugs prescribed by doctors (Rensberger, 1976).

In contrast, it has been suggested that drugs are remarkably nontoxic, considering their extensive use (Jick, 1974). According

to data from the Boston Collaborative Drug Surveillance Program, death from drugs occurs in less than 0.3% of hospitalized medical patients in the United States, and for each course of drug therapy the frequency of adverse drug reactions is only 5%, or one in 20 treatments. Furthermore, although associated with discomfort, most drug reactions—such as nausea, drowsiness, diarrhea, vomiting, and rash—are transient and of minor consequence to the patient. Others have rejected both positions, arguing that estimates of the magnitude of the problem of adverse drug reactions are characterized by incomplete, arbitrary, and uncontrolled data and by unreliable and inaccurate cost estimates (Karch and Lasagna, 1975).

In the context of unresolved controversy, the issue of adverse reactions to drugs in the elderly must be considered. The extent to which age itself is a risk factor for untoward therapeutic events is uncertain and has been the subject of several critical reviews (Gardner and Cluff, 1970; Klein et al., 1981; Nolan and O'Malley, 1987b; Vestal et al., 1985).

Not all the studies agree, but many have demonstrated a higher incidence of adverse drug reactions in hospitalized geriatric patients. In studies in which an age-related increase was observed, it ranged from 1.6-fold to 5-fold. Patients over 70 appear to be particularly vulnerable, with an incidence of about 20%, compared with 3–10% in patients under 30 (Hurwitz, 1969; Seidl et al., 1966). Studies performed in the United States (Seidl et al., 1966), Northern Ireland (Hurwitz, 1969), New Zealand (Smidt and McQueen, 1972), Switzerland (Klein et al., 1976), and Israel (Levy et al., 1977) have consistently documented an association between age and an increased incidence of adverse drug reactions.

The data on outpatients are limited. Two studies demonstrated an increase with age (Kellaway and McCrae, 1973; Lumley et al., 1986) and two demonstrated no effect of age (Klein et al., 1984; Mulroy, 1973). In one of the studies that did not show an age effect, the results suggested that the elderly might be unable to distinguish drug side effects from symptoms of “old age” and unable to communicate adverse effects to their providers (Klein et al., 1984).

Limitations of the data on adverse drug reactions in the elderly have been enumerated (Klein et al., 1981; Nolan and O'Malley, 1987b; Vestal et al., 1985). Most studies have involved hospitalized patients. True populations at risk, which would include patients

taking drugs in the community as well as patients in the hospital, frequently have not been studied. Patients have not been stratified according to severity of illness or concurrent drug therapy. Unmedicated control groups have not been included.

Despite the limitations, the available data indicate that several risk factors are associated with adverse drug reactions, including age, sex, drug dosage, previous drug reaction, impairment in hepatic or renal function, length of hospital stay, and multiple-drug therapy (Vestal et al., 1985). In addition, age differences in physiology and pharmacology might help to explain the apparent propensity of the elderly to suffer adverse reactions to drugs.

LIFE-STYLE

Deliberate Chemical Exposure

Life-style is important in determining the types and quantities of chemical agents (other than pharmaceuticals) that are deliberately brought into contact with the human body. Some of the agents reflect cultural trends, others are more individual.

The chemicals and their uses are diverse. Specialized components of the diet have become popular in the United States, although scientific data to justify their use are generally lacking. Some people are convinced of the merits of an exclusively or predominantly vegetarian diet; others use supplements that include pure preparations of vitamins, amino acids, minerals, and other compounds, as well as many complex chemical mixtures represented by "unusual" plant and other materials or extracts. Whether such materials have any effect on the aging processes, either adverse or beneficial, generally has not been tested. Similarly, their toxic effects are usually unstudied.

Another important source of deliberate human exposure to chemical agents comes from the use of various types of fragrances and cosmetic agents. These are often complex chemical mixtures whose major and minor components are untested beyond acute toxic potential. Studies involving repeated application to the skin of experimental animals have sometimes revealed dermal and neurologic damage.

Deliberate chemical exposure of human subjects occurs in a number of other settings, many of which are influenced by individual preferences and life-style—for example, use of mouthwash and

oral deodorants, antiseborrheic shampoos, sunscreen and suntan lotions, and insect repellents.

Learned Helplessness

Aging is associated with a loss of control over homeostatic responses, mobility, and cognitive function, for example. In physiologic terms, the loss of control leads to a narrowing of homeostatic reserve and, in behavioral terms, to helplessness. The tendency of family and friends, as well as members of the health professions, to urge accommodation rather than resistance to progressive incursions on functional capacity leads to "learned helplessness." The acceptance of helplessness leads not only to greater helplessness, but also to increased susceptibility to disease.

A dramatic example of the relationship between learned helplessness and disease occurs in rats subjected to the "yoked" electric-shock paradigm of Weiss (Sklar and Anisman, 1979; Visintainer et al., 1982). Two rats are connected (yoked) in series to a random electric-shock generating system. Both rats have levers in their cages, but only one lever functions as a switch for the electric circuit. When the functional switch is pressed, the electric shock to both rats is turned off. However, only the rat with the functional switch is in control; the other is subjected to "learned helplessness." A third rat is placed in the cage, but is not subjected to electric shock. The effect of these environmental manipulations on susceptibility to disease is striking. For example, if the dose of cancer cells that kills 50% of the rats not subjected to electric shock is given to rats that have learned helplessness, 80% of the animals die. The same dose of cancer cells kills only 20% of the rats in control.

It seems reasonable to conclude that some of the increased intrinsic susceptibility to disease that is manifested in the elderly could be related to environmental influences that result in learned helplessness among physiologically compromised and behaviorally impaired people.

Atrophy of Disuse

Life-style can inevitably affect aging processes and the aged

through occupation, recreational activities, exercise habits, eating and drinking habits, tobacco smoking, exposure to stress— almost any behavior that creates contact between the person and the environment. Elements of life-style can increase or decrease risks of acquiring age-related degenerative diseases. They can also conceivably accelerate or delay physiologic and anatomic changes associated with the passage of years. Clear examples are the variety of age-related diseases induced by toxic chemicals in tobacco smoke and the decrease in risk of cardiovascular disease produced by regular exercise.

Atrophy of disuse is a consequence of life-style and therefore belongs among factors responsible for extrinsic aging. Decline in the vigor, health, and well-being of the aging and the aged is tacitly assumed to be due to intrinsic aging, but these unfavorable changes result largely from atrophy of disuse. The debilitated state resulting from atrophy of disuse conceivably contributes to susceptibility to age-related diseases; however, such effects are difficult to dissect from the general complex of events that make up intrinsic and extrinsic aging.

In a study of some 17,000 middle-aged and older Harvard alumni over several years, Paffenbarger et al. (1984) found a 49% excess risk of coronary heart disease among people who led sedentary life-styles (Butler and Lewis, 1986).

Indoor Pollutants

The indoor environment is a subject of growing concern. During the last decade, health experts and regulatory officials have recognized that indoor exposures can have a greater effect on human health and comfort than outdoor pollutants. Americans spend up to 80% of their time indoors—in homes, in public buildings, in offices or other places of work, or in various modes of transportation. Those who are most susceptible to the health effects of pollution —the very old, the very young, and the chronically ill—might spend even more of their time indoors.

No federal standards for indoor air—apart from industrial workplace standards—exist. Yet the concentrations of some pollutants in office buildings, homes, and public places are known to exceed their primary ambient-air quality standards. Modern energy-conservation measures that reduce ventilation can cause “sick buildings” and the related health effects.

Indoor pollutants of concern identified by the National Research Council (1981a) and in other reports include radon and its decay products, asbestos, tobacco smoke, formaldehyde and other organic compounds, the gases from combustion (principally nitrogen dioxide and carbon monoxide), and microorganisms and allergens. There is little epidemiologic information on the health effects of chronic, low-level exposure to any of these pollutants except tobacco smoke (National Research Council, 1986). What data exist have been derived principally from occupational exposures—to uranium, pesticides, and asbestos, for example—and most involve acute exposures.

For some pollutants, human discomfort provides a useful indicator of environmental contamination. Discomfort gives immediate incentive to avoid or correct environmental deficiencies and can lead to closer investigation of their source. Unfortunately, the populations that are most susceptible to the effects of pollution might be the least able to do anything about it. The elderly commonly have diminished sensory perception and are less able to detect contaminants in their environment. People who seldom go outside into fresh air or who are chronically exposed to carbon dioxide or carbon monoxide might also have diminished sensory capacity.

Temperature

Conditions for thermal comfort appear to vary little, if at all, with such factors as geographic location, sex, ethnic background, and even age (Fanger, 1972). Aging merits some special consideration: the basal metabolic rate decreases progressively, but evaporative heat loss does also. These two changes tend to offset each other to a limited extent that is difficult to assess, because the elderly spend much more time than the young in sedentary activities. Furthermore, with the energy conservation practices now common indoors during winter, the elderly have a narrower temperature range, which limits their thermal resistance (Sacher, 1979).

Sensory adaptations in sedentary older persons might be severely diminished, and a person could fail to notice the symptoms of impending hypothermia until they became severe.

Radon

The radioactive gas radon and its decay products have drawn considerable attention in recent years after discoveries of very high indoor concentrations in some parts of the country. Exposure to high concentrations of radon and its progeny causes lung cancer.

Most of the data on the health effects of radon progeny come from studies of underground miners whose occupational exposures were 100–1,000 times those of the general population. However, homes in some locales have recorded radon concentrations higher than those in mines. Data on Canadian uranium miners indicate an excess of lung cancers even in the group with the lowest cumulative dose—a dose that would be in the same range as the lifetime cumulative dose from many home exposures.

A few epidemiologic studies of nonoccupational radon exposure have been done, but most have failed to control for smoking. However, it appears that both active smoking and passive smoking increase susceptibility to the effects of radon, because radon progeny adhere to respirable particulate matter in tobacco smoke. Nero et al. (1986) recently reviewed the associated risks.

Formaldehyde

There are many sources of formaldehyde exposure in the indoor environment. Particleboard, paneling, plywood, and ureaformaldehyde foam insulation can be important sources of vapors. Because of their extensive use of particleboard, with its high surface-to-volume ratio, mobile homes have been found to have much higher concentrations of formaldehyde than conventional homes. In addition, cosmetic products, especially shampoos, are a source of skin exposure, and cigarette smoke contains 10–15 mg of formaldehyde per cigarette.

Formaldehyde, a contaminant of concern to all populations, might be particularly important in the health and comfort of elderly people and people with chronic respiratory problems. The present Occupational Safety and Health Administration standard for formaldehyde is 3 ppm. However, the National Institute for Occupational Safety and Health has recommended that occupational exposure be reduced to the lowest feasible, to minimize the risk of cancer (U.S. NIOSH, 1981). Potential carcinogenicity has been reviewed by the International Agency for Research

on Cancer (1982). In addition, people have reported mild ear, nose, and throat discomfort and other symptoms at less than 0.5 ppm. Between 10 and 20% of the general population might be susceptible to the effects of formaldehyde and react acutely at any concentration.

The principal effect of formaldehyde at low concentrations is irritation of the eyes and mucous membranes. Human eyes are very sensitive to airborne formaldehyde; they can be irritated by atmospheric concentrations of 0.05–0.5 ppm and in some cases respond to 0.01 ppm when formaldehyde is mixed with other pollutants. At relatively low concentrations (0.1 ppm), it can irritate upper airways; it more frequently does so at 1–11 ppm (NRC, 1981a). In some susceptible persons, an allergic reaction might occur at very low concentrations, causing bronchoconstriction and asthmatic symptoms.

Combustion Products

The two indoor combustion products that most often cause concern about health effects on those exposed are nitrogen dioxide (NO_2) and carbon monoxide (CO). The amount of NO_2 formed in unvented indoor combustion devices is not usually sufficient to cause acute toxicity; however, NO_2 concentrations equal to or greater than the current ambient-air quality standard of 0.05 ppm are not unusual in kitchens with gas cooking (NRC, 1981a). In animal studies, NO_2 has been shown to produce transient and long-term damage to small bronchial airways and alveolar tissue (WHO, 1977). In addition, changes in nonciliated cells, destruction of Type I epithelial cells, and proliferation of Type II cells after relatively low exposures (2 ppm for 4 hours) suggest that chronic exposure could lead to chronic bronchitis and the development of emphysema (Evans and Freeman, 1980). Resistance was weakened in animals chronically exposed to NO_2 at low concentrations with bacterial aerosol challenge (Gardner et al., 1979).

A 1981 study by Mostardi et al. compared the health of children attending two schools, one of which bordered an industry and had comparatively high concentrations of NO_2 and sulfur dioxide. The study found a higher incidence of acute respiratory illness and significantly compromised pulmonary function among the children attending the school near the industry. That finding is important

because recent evidence has suggested that frequency and severity of acute respiratory illness in childhood are related to chronic obstructive lung disease in adulthood.

The second important product of combustion, CO, is found in cigarette smoke and fossil-fuel combustion effluents, and thus is found commonly indoors in a broad range of concentrations. The principal health effect of CO is impaired oxygen transport. CO is readily absorbed from inspired air and binds to hemoglobin with over 200 times the affinity of oxygen. Doses are cumulative, so exposure to CO at even low concentrations in the air can result in substantial carboxyhemoglobin concentrations in the blood. Although healthy people are not greatly affected by exposure to CO at low concentrations, those with limited cardiovascular reserve can be at greater risk because their blood has reduced oxygen-carrying capacity. In addition, CO has been implicated in the pathogenesis of atherosclerosis.

Asbestos

Asbestos has been widely used in public and private buildings, in insulation and fireproofing materials, in ornamental decoration and soundproofing, and on surfaces in public areas. An extensive program has recently been undertaken to identify and remove it from school buildings.

The relationship between exposure to asbestos and lung cancer is well known. Asbestosis, mesothelioma, and gastrointestinal tract cancers have been found in excess among workers occupationally exposed to asbestos. Less is known about the health effects of exposures to asbestos and other fibrous materials in environments other than the workplace.

Environmental Tobacco Smoke

Tobacco smoke is a major source of pollution in the indoor environment. Nonsmokers absorb measurable amounts of CO and nicotine and can absorb small amounts of other constituents from environmental tobacco smoke (ETS). ETS contains several other known hazardous pollutants, but few studies have been done on exposure to them by this route.

Many of the chemicals identified in cigarette smoke are irritating to the nose, throat, and eyes. Studies of the long-term effects

of passive smoking have suggested that it can cause small-airway dysfunction, which is an early precursor of clinically important chronic obstructive lung disease. Exposure to ETS appears to cause some increase in systolic blood pressure, especially in children. As mentioned above, carboxyhemoglobin concentration can be increased by exposure to tobacco smoke, which would reduce the maximal exercise capacity in normal adults. Some people are allergic to ETS, although documentation on the numbers of these people is inadequate.

Chronic exposure to tobacco smoke apparently can impair immune system function. Laboratory studies on mice have found that chronic tobacco-smoke exposure accelerated many of the immunologic changes associated with aging, including marked modifications of the responses associated with the T-lymphocyte arm of the immune system and of the systemic clearance mechanisms.

Populations that might be more susceptible than others to the effects of ETS include children, people with coronary arterial disease, and people with chronic lung disease. Patients with compromised heart or lung function suffer earlier onset of angina or dyspnea, respectively, after exposure to ETS.

Pesticides

A wide variety of pesticides are available for use in the home and in public and office buildings. They are assumed to be an important source of exposure to known hazardous substances. About 9 of 10 households in the United States use some type of pesticide in the house, garden, or yard; nearly 84% of this use is in the house. A study conducted in South Carolina (a region of heavy pesticide use) by Kiel et al. (1969) found that one-third of the families that used pesticides applied them during each week of the year. A study by Savage et al. (1981) surveyed 10,000 households in different regions of the United States and found over 500 pesticide formulations being used. Many people did not know what pesticide they had used (e.g., “bug spray”). Interviews with members of 8,254 households yielded the recording of use or storage of 1,756 containers of unknown insecticides.

6

Environmental Effects on Age-Associated Diseases and Changes in Organ Function

Biologic changes associated with aging can reasonably be expected to be associated with parallel changes in susceptibility to disease. For some diseases, such as those for which early antigenic stimulation produces lifelong immunity, resistance usually increases and incidence falls with age. For other diseases, such as those reflecting cumulative, chronic exposures, rates might increase with age.

Susceptibility to disease changes throughout the human life cycle and is believed to be a function of many factors, including changes in the immune system and in the rate of cellular division. Thus, exposures to carcinogens or neurotoxins in infancy and childhood (or in old age) might produce stronger responses than those occurring in the middle stages of life. Although there are reasonable theoretical grounds for expecting some disease patterns to be normal functions of age, additional research needs to be done to clarify possible mechanisms. Controlled studies of animal populations are also needed to determine both the natural occurrence of diseases with aging and changes in immune response and in metabolic and kinetic responses to xenobiotics throughout the life cycle.

This chapter reviews some of the animal and human studies on the relationships of the environment with age-associated

diseases in specific organ systems. It also discusses evidence of age-associated changes in normal functions, such as vision, bone metabolism, and the immune system. Table 6–1 presents some examples.

TABLE 6–1 Examples of Age-Associated Changes in Organ Structure and Function and Possible Related Agents, Medical Conditions, or Life-styles

Organ or System	Agent, Medical Condition, or Changes in Organ Structure and Function Often Associated with Old Age	Life-style Possibly Related to Changes in Organ Structure or Function
Skin	Coarseness, wrinkling, malignant neoplasms, immune suppression	Sunlight
Eye	Cataracts	Sunlight
	Cataracts, retinopathy	Diabetes
Ear	High-frequency hearing loss	Noise
Nervous system	Dementia, confusion	Anticholinergics, barbiturates, bromide
	Peripheral neuropathy	Acrylamide, vincristine, isoniazid
	Parkinsonism	MPTP
	Amyotrophic lateral sclerosis, parkinsonism, senile dementia of Alzheimer's type	Chamorro life-style (cycad exposure?)
Renal	Increased nephropathy	Reduced dietary protein
Immune	Reduced decline in immune competence	Reduced caloric intake
	Exacerbation of autoimmune reactions	Procainamide, estrogen
Lung	Emphysema, cancer	Cotton dust, tobacco smoking
Cardiovascular	Atherosclerotic heart disease	Dietary lipids

DEMOGRAPHICS OF AGE-ASSOCIATED DISEASES

Age seems to be the most important determinant of incidence of most human diseases. Characteristic age patterns of risk have been described for all diseases, and many of the patterns have provided the basis for important etiologic theories. For example, the peak in incidence of one type of Hodgkin's disease in the third decade of life suggested an infectious origin (MacMahon, 1971),

and the plateau in incidence of breast cancer around the ages of 45–55 suggested an effect of the cessation of ovarian function on the development of the disease (Petrakis et al., 1982). The premenopausal and postmenopausal incidence curves for breast cancer in different countries suggest that environmental factors play more important roles in the etiology of postmenopausal breast cancer, whereas genetic, endocrinologic, and other endogenous factors strongly influence premenopausal disease (Figure 6–1).

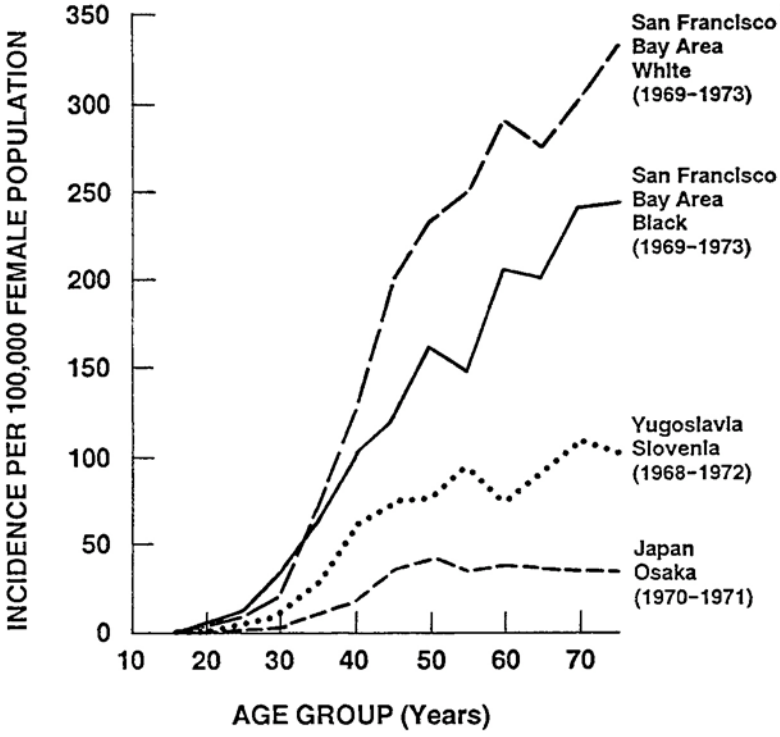

FIGURE 6–1 Age-specific incidence rates for female breast cancer in four population groups. Source: Petrakis et al. (1982).

The role of age as a factor associated with increasing incidence appears to be direct (or independent) in some diseases. In others, time and age-associated exposure characteristics, such as obesity and duration of exposure, are the direct factors, and not age itself. The association of disease susceptibility with age—which might be related to intrinsic factors, extrinsic factors, or some combination—needs to be assessed for each disease. For example,

the role of specific intrinsic and extrinsic factors in adult-onset diabetes mellitus has been extensively investigated, but further studies are needed for an adequate understanding of the relative importance and interaction of endogenous and exogenous factors in the disease.

Both morbidity and mortality data can be used to evaluate the association of disease with age in the elderly population (65 and over). Morbidity data reflect either the incidence (new cases) of a disease over a fixed period or its prevalence (total cases) at a given time, depending on the study design or the method of data collection. These two measures of disease frequency (incidence and prevalence) provide different information, and both are important—one for an understanding of the population risk (incidence) and one for an understanding of the burden (prevalence) of a particular disease. Mortality data, which are more readily available than morbidity data for the total population, parallel incidence data for conditions that are life-threatening and of short duration, such as some forms of cancer and cardiovascular disease, but are not as useful for other diseases, such as diabetes and chronic obstructive pulmonary disease.

Two-thirds of all deaths in the United States occur in people over age 65, and 30% occur in persons over 80. Three causes of death—heart disease, cancer, and stroke—accounted for 75% of these deaths in the elderly population in 1979 and in 1950 (NCHS, 1981b). Two features of the recent cause-specific mortality patterns in the elderly are of interest here—the decline in mortality rates for cardiovascular and cerebrovascular diseases among the elderly and the maintenance of those rates for cancer (Figure 6–2). From 1950 to 1979, the overall mortality rate for the population 65 and over decreased by 17%. When rates are age-adjusted (to allow for the rapid increase in the population 85 and over), mortality declined more than 27% and the decline for females was twice that for males (Figure 6–3).

Mortality from heart disease accounted for approximately half the overall decline during the period, and that from cerebrovascular disease accounted for another 25% of the overall decline. Heart and cerebrovascular diseases account for the largest and third largest mortality rates, respectively, in this age group. Cancer mortality, the second largest element and the only major one to show an increase, increased by 13%. More than half the deaths from cancer among the elderly are due to cancers of the lung,

colon, genital organs, and breast (females). Cancer mortality trends among males indicate a slight deceleration in the large annual increases in lung cancer mortality and slowly increasing rates for cancers of the colon and prostate. In contrast with the increase in overall cancer mortality in males, the overall cancer mortality rate in women 65 and over decreased slightly from 1950 to 1978 (Figures 6–4 and 6–5). The most obvious changes for females are the large increase in lung cancer mortality and the decreases in mortality from cancers of the stomach and uterine cervix.

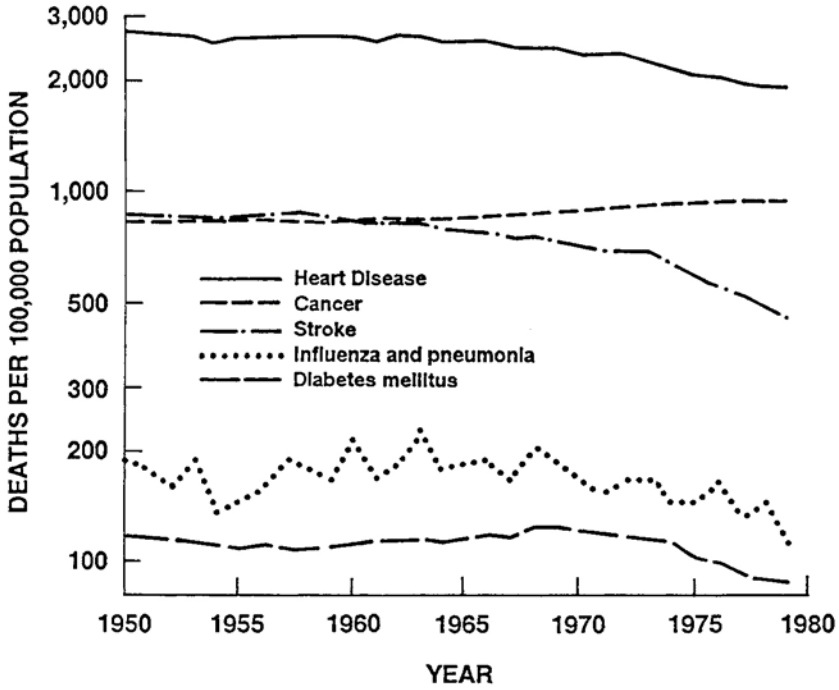

FIGURE 6–2 Age-adjusted death rates for persons 65 years of age and over, according to leading causes of death: United States, 1950–1979. Source: National Center for Health Statistics (1982).

An exponential increase in mortality with age is evident for cardiovascular disease (Figure 6–6), but absent for all cancers combined (Figure 6–7). In fact, cancer mortality rates (all sites combined) increase rapidly in middle age and then more slowly with age to 65. Between ages 65 and 69, cancer accounts for approximately 30% of all deaths; by age 80, it accounts for only 12%. In

contrast, the proportion of deaths caused by cardiovascular disease increases from 50% at ages 65–69 to 65% by age 80. Brody (1983, 1987) has suggested that the modest increase in age-specific mortality rates for cancer after age 65 might constitute evidence that cancer pathogenesis is not closely related to the aging processes and host susceptibility, and that by the year 2000 cancer will account for fewer than 10% of the deaths in those 85 and over—the age group that will experience half of all deaths.

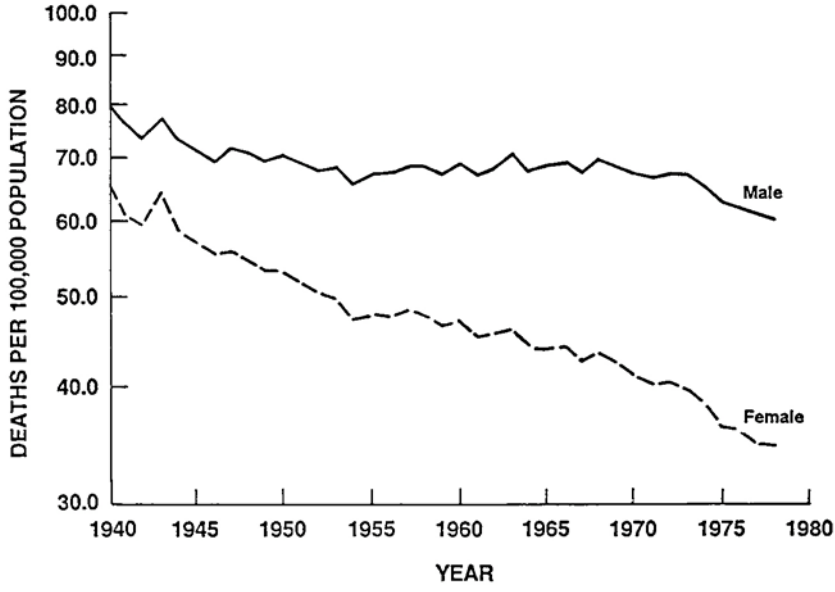

FIGURE 6–3 Age-adjusted death rates for persons 65 years of age and over, according to sex: United States, 1940–1978. Source: National Center for Health Statistics (1981b).

Before epidemiologic observations associating cancer mortality with aging processes can be fully evaluated, several considerations are essential. Smoking is the most likely cause of the increase in respiratory cancer mortality, and cancer mortality in general, among elderly men and women. Although a higher proportion of elderly men than women smoke, the sex gap in smoking behavior has narrowed considerably in recent years. The proportion of men 65 and over reported as current smokers dropped from 28.5% in 1965 to 17.9% in 1980; the proportion of women increased from 9.6% to 16.8%. The sex differences for former smokers, which could be more important for respiratory cancer, are even greater:

the proportion of men 65 and over reported as former smokers increased from 28.1% in 1965 to 47.4% in 1980, and the proportion of women increased from 4.5% to 14.2%.

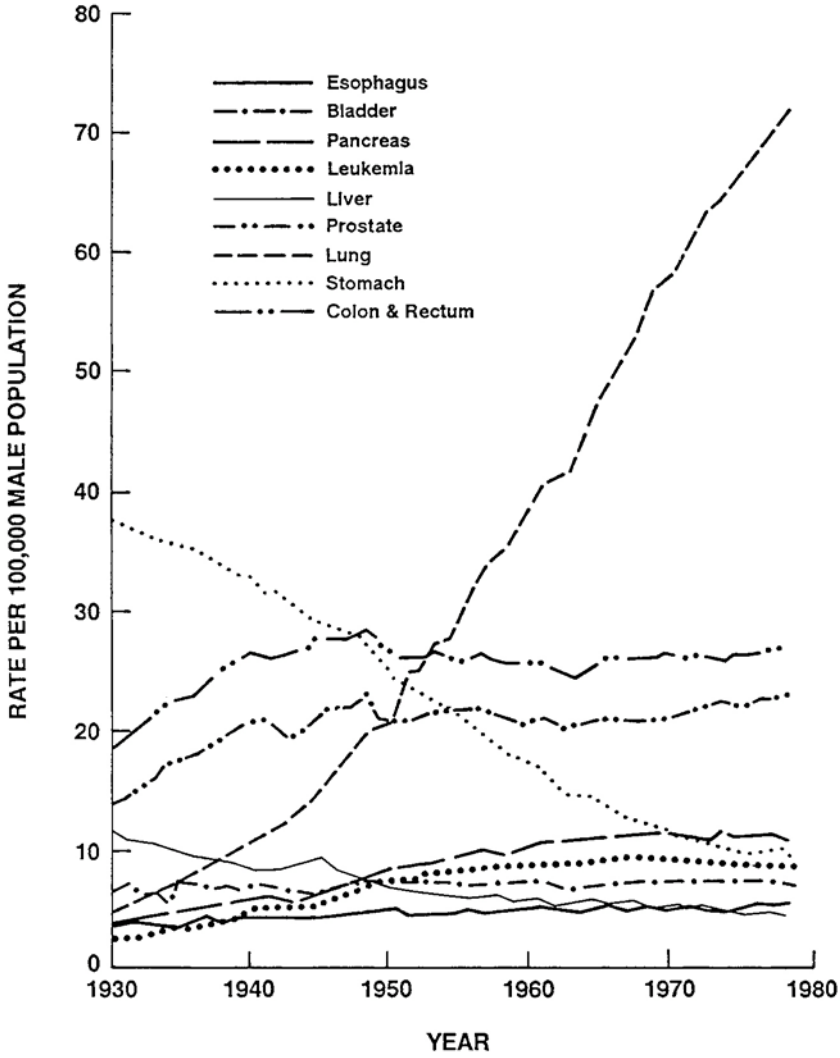

FIGURE 6–4 Age-adjusted cancer death rates for selected sites, males: United States, 1930–1978. Source: U.S. OTA (1985).

Differences in smoking among and between elderly men and women no doubt account for some of the observed differences

in cancer mortality, especially respiratory cancer mortality. It is estimated that cigarette smoking alone accounts for 80–85% of lung cancer mortality and 30% of all cancer mortality (Doll and Peto, 1981).

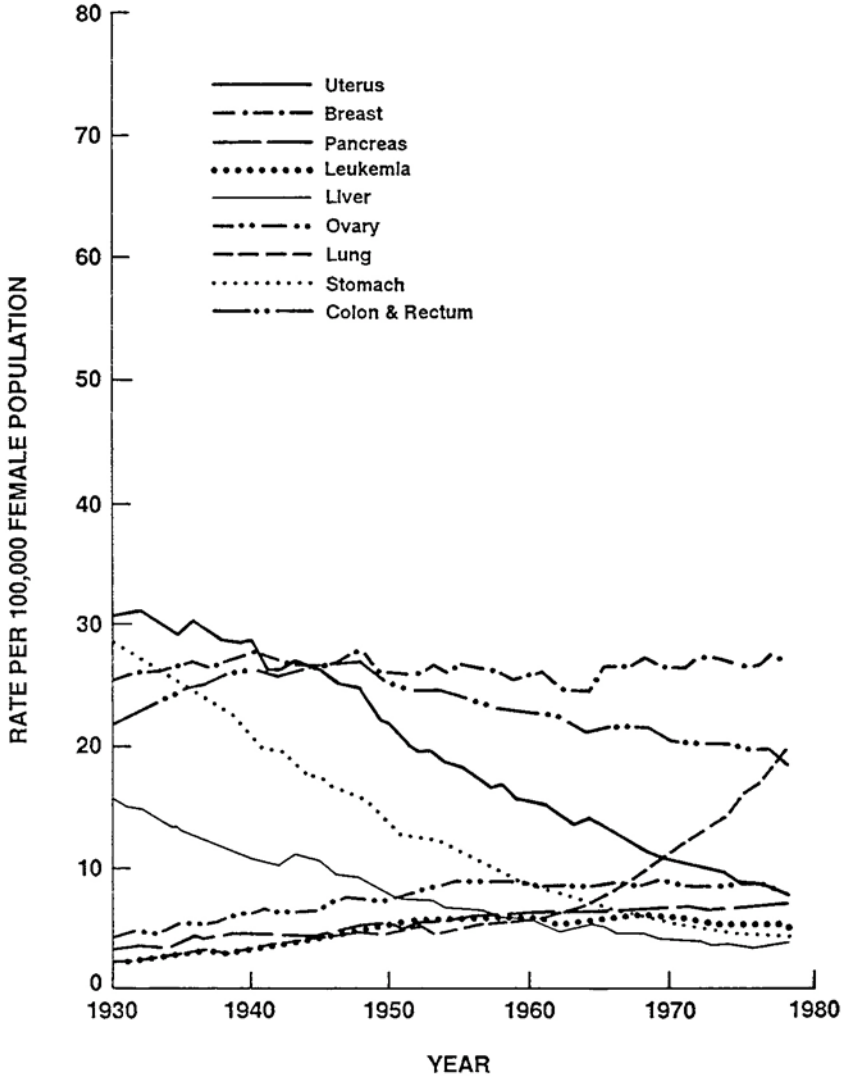

FIGURE 6–5 Age-adjusted cancer death rates for selected sites, females: United States, 1930–1978. Source: U.S. OTA (1985).

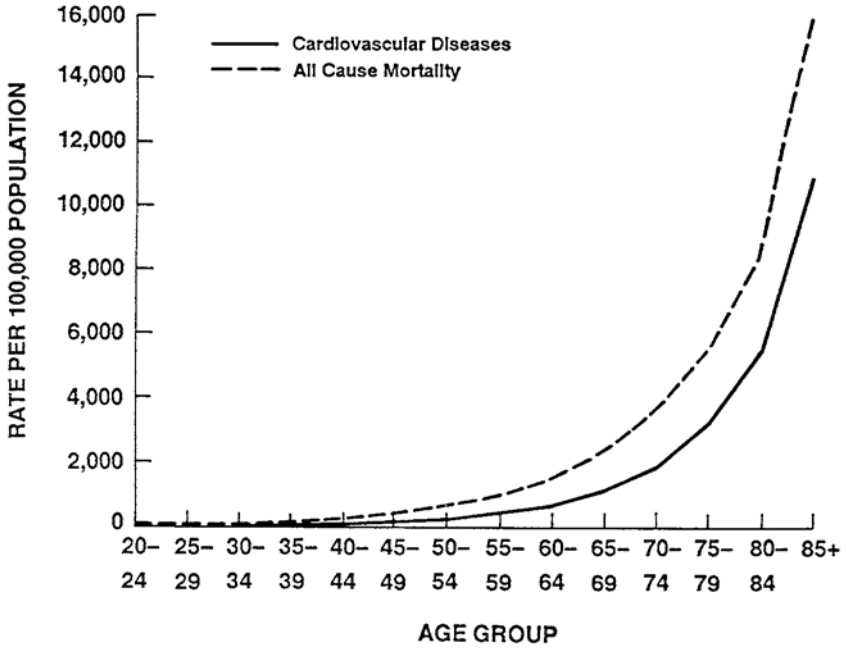

FIGURE 6–6 Major cardiovascular diseases: age-specific mortality rates versus all causes of mortality. Source: National Center for Health Statistics (1985a).

It has been suggested that the reason for the rising incidence of cancer with increasing age might be aging of the immune system itself, but the available epidemiologic evidence does not support this view except for some tumors. Because increasing age is associated with many time-related factors, including longer exposure to carcinogens, it is difficult to separate the effects of increasing age from the effects of increased exposure to carcinogens.

Two lines of evidence, however, can address the effect of age itself on cancer incidence. Peto et al. (1975) conducted a large, controlled study in mice at various ages whose skin was exposed to benzo[a]pyrene. The incidence of epithelial cancers was independent of age at the start of exposure and was related directly to duration of exposure. A recent review of the available experimental evidence from animals (Hornig, in press) found little support for the notion of a general increase in susceptibility to the effects of all carcinogens with increasing age. In addition, the presence

of such factors as time-related cumulative damage and the physiologic changes associated with aging that can affect susceptibility makes it apparent that there might not be a single answer to the question of the relation between increasing age and cancer susceptibility, and that the relation varies with target organ, cell type, toxic exposure, and animal species (Birnbaum, 1987).

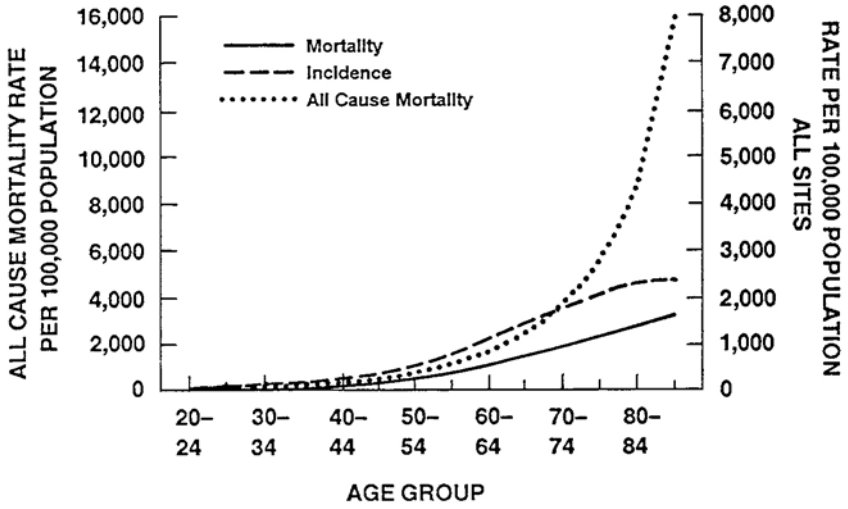

FIGURE 6–7 All sites: age-specific cancer incidence and mortality rates versus all causes of mortality. Adapted from Brody (1983) and Brody and Brock (1985).

Epidemiologic evidence supports the hypothesis that the increase in lung cancer risk with age is independent of the smoking-related increase in risk. The effect of exposure duration can be estimated by noting the increase in incidence over time, measured from the start of smoking in smokers and from birth in nonsmokers; the incidence rates are similar over time. However, the effect of age can be estimated by noting incidence over time, measured from birth in all subjects; the incidence increases more rapidly in smokers over time (Doll and Peto, 1978; Peto and Doll, 1984).

As noted by Doll (1978), the tumors for which immune factors are important, such as non-Hodgkin's lymphoma and soft-tissue sarcomas in patients treated with immunosuppressive drugs, are tumors of mesenchymal origin whose incidence does not rise steeply with age, as is observed with the common epithelial cancers. The

very prompt rise in the incidence of lymphomas in transplant recipients after treatment with immunosuppressive agents is in marked contrast with the long induction times observed for epithelial tumors resulting from exposure to chemical carcinogens (Hoover and Fraumeni, 1973). Those observations suggest a different, possibly viral, etiologic process for the mesenchymal tumors that are associated with immune factors. The increased incidence of squamous carcinoma of the skin in patients receiving immunosuppressive agents suggests that this epithelial tumor is also under immunologic control (Kripke, 1974).

TABLE 6–2 Death Rates for the 10 Leading Causes of Death for Ages 65 and Over, by Age, 1976

	Deaths per 100,000			
Cause of Death	65 Years and Over	65–74 Years	75–84 Years	85 Years and Over
All causes	5,428.9	3,127.6	7,333.6	15,486.9
Heart diseases	2,393.5	1,286.9	3,263.7	7,384.3
Malignant neoplasms	979.0	786.3	1,248.6	1,441.5
Cerebrovascular diseases	694.6	280.1	1,014.0	2,586.8
Influenza and pneumonia	211.1	70.1	289.3	959.2
Arteriosclerosis	122.2	25.8	152.5	714.3
Diabetes mellitus	108.1	70.0	155.8	219.2
Accidents	104.5	62.2	134.5	306.7
Motor vehicle	25.2	21.7	32.3	26.0
All other	79.3	40.4	102.2	280.7
Bronchitis, emphysema, and asthma	76.8	60.7	101.4	108.5
Cirrhosis of liver	36.5	42.6	29.3	18.0
Nephritis and nephrosis	25.0	15.2	34.1	64.6
All other causes	677.5	427.8	908.6	1,638.8

SOURCE: National Center for Health Statistics (1978a).

Mortality rates by age group for diseases of the heart, influenza and pneumonia, cerebrovascular disease, arteriosclerosis, and accidents show a marked increase in risk with increasing age, whereas rates for other causes—such as cancer, diabetes mellitus, bronchitis, emphysema and asthma, and nephritis and nephrosis— indicate a more modest increase (Table 6–2). Mortality due to cirrhosis of the liver does not appear to be associated with increasing age in the elderly population.

TABLE 6–3 Prevalence of Selected Impairments by Age and Sex, United States, 1981

	Prevalence, Number of Persons per 1,000	
Condition	All Ages	65 or Older
Visual impairment	40.4	136.6
Hearing impairment	82.9	283.6
Paralysis (complete or partial)	5.9	19.6
Heart conditions	76.4	277.0
Hypertensive disease	113.4	378.6
Cerebrovascular disease	8.3	45.4
Chronic bronchitis	35.3	46.1
Emphysema	9.3	42.9
Functional or symptomatic upper gastrointestinal tract disorders	17.4	39.9
Diverticula of intestine	6.8	38.4
Diabetes	24.3	84.8
Urinary system disease	25.9	56.6

SOURCE: National Center for Health Statistics (1981b). Based on household interviews of noninstitutionalized civilians.

The prevalence of every chronic condition studied in the National Health Interview Study is higher among those 65 and over, and the estimates no doubt understate the age effects in that they do not include the elderly who are in nursing homes (Table 6–3).

As early as the 1960s, accumulating evidence was showing that cardiovascular risk factors could be modified to change the risk of morbidity and mortality (Hypertension Detection and Follow-up Program Cooperative Group, 1985, 1987; Langford et al., 1986; Multiple Risk Factor Intervention Trial Research Group [MRFIT], 1982, 1986; Paffenberger, 1979; Paffenberger et al., 1978; U.S. Public Health Service, 1968; Veterans' Administration Cooperative Study Group, 1967, 1970; Wald, 1976).

Research on human aging processes and the impact of environmental factors has been increasingly constrained by declining autopsy rates. Many reasons have been given for the decline in autopsy rates (American Medical Association, Council on Scientific Affairs, 1987), including the fact that the Joint Commission on the Accreditation of Hospitals (JCAH) no longer requires a minimal rate of autopsy for accreditation. At present, only 14–15% of all

deaths in hospitals are subjected to autopsy, whereas 30–40 years ago it was approximately 50% (Guariglia and Abrahams, 1985). The Institute of Medicine statement on national autopsy policy emphasized the essential role of autopsy (Mortimer, 1985). Earlier studies showed that autopsy rates were lower for deaths occurring among older persons than among younger persons, and the difference appears to have persisted. Present autopsy rates might be as low as 1% for deaths among persons over 65.

This trend results in a loss of important pathologic information for studies of human aging—information for which there is no substitute (Kohn, 1982). In the absence of postmortem studies, epidemiologic studies of age-associated diseases and mortality must rely on predeath diagnoses or cause-of-death statements on death certificates. For some causes of death, the death- certificate information might be inaccurate for as many as 50% of deaths. In addition, the existence of a system to ensure the collection, study, and storage of relevant tissues, cells, and body fluids would support studies of body burdens of environmental agents and the consideration of potential causal associations of these agents with tissue changes.

SKIN

Environmental factors are widely suspected of contributing to the effects of the aging processes and to age-associated pathologic conditions, but there are few examples. Among the best documented is photoaging—the changes in skin appearance and function that are due to habitual exposure to the sun rather than to the passage of time alone.

Photoaging, also called premature aging and dermatoheliosis, is virtually synonymous in the public mind with “true” chronologic aging and has only recently been differentiated, even by dermatologists (Gilchrest, 1984). Clinically, photoaging is characterized by coarseness, wrinkling, mottling, laxity, telangiectasia (dilation of blood vessels), atrophy, fibrotic depigmentation (pseudoscars), and ultimately malignant neoplasia on the face, neck, hands, and other habitually exposed body areas. Fair-skinned people living in areas of high insolation (solar intensity) and having extensive vocational or recreational sun exposure are affected earliest and most severely, but most white Americans manifest the changes to

some degree by the fifth decade and many by the third decade. Clinical changes are generally progressive throughout life.

Cigarette smoking is a second environmental factor that has been repeatedly noted to produce premature aging of the skin, most recently in a prospective blinded study controlled for age, social class, exposure to the sun, and recent weight change (Model, 1985). Among 116 patients aged 35–69, those who had smoked at least 10 cigarettes per day for at least 10 years were far more likely than nonsmokers to have deeply wrinkled, atrophic, leathery skin. Unfortunately, the probable adverse effect of smoking on cutaneous aging has not been examined in animal or cell-culture experiments.

Substantial epidemiologic data and experimental animal data have implicated the ultraviolet (UV) portion of sunlight, particularly UVB (290–320 nm), in both photoaging (Kligman, 1969; Kligman et al., 1982; Smith et al., 1962) and photocarcinogenesis (Blum, 1959; Urbach et al., 1974). Longer UV wavelengths and even infrared (heat) energy might also contribute (Kligman et al., 1985; Strickland, 1986). No data either support or exclude interactions between UV radiation and other (e.g., chemical or dietary) environmental exposures in those processes.

Photoaging has been estimated to account for more than 90% of age-associated cosmetic skin problems (Gilchrest, 1984), which affect people's self-esteem (Graham and Kligman, 1985) and society's perception of them (Dion et al., 1972). Extensive epidemiologic data support a causal role of photoaging in a similar percentage of basal cell and squamous cell carcinomas (Urbach et al., 1974), which together account for more than half of all malignancies in the United States. Exposure to the sun is also implicated in a smaller (but unknown) percentage of cases of malignant melanoma (Lancaster and Nelson, 1957; Magnus, 1977; Movshovitz and Modan, 1973), a major public-health concern because of its rapidly increasing incidence (Jensen and Bolander, 1980) and substantial fatality rate.

Apart from its universal adverse long-term effects on appearance and its major role in skin carcinogenesis, habitual exposure to the sun has recently been recognized as exacerbating several of the more subtle age-associated functional losses in human skin. One example of probable medical importance is immune responsiveness. Both establishment and expression of delayed hypersensitivity in the skin are impaired in the elderly (Smith et al., 1962; Waldorf et al., 1968). The impairment is attributable in part to

the well-known age-associated decreases in T-lymphocyte function (Mackay, 1977).

In addition, age-associated decreases in the number of epidermal Langerhans cells, the bone-marrow-derived cells responsible for immune expression in the skin, have been measured (Gilchrest et al., 1982b; Thiers et al., 1984). Two studies that used different histologic techniques have documented a further 20–50% reduction in Langerhans cells in skin habitually exposed to the sun (Gilchrest et al., 1983; Thiers et al., 1984), and a third study has revealed a similar decrease in the ease of allergic sensitization to dinitrochlorobenzene in adjacent sun-exposed versus sun-protected skin sites in elderly volunteers (O'Dell et al., 1980). According to the immune-surveillance theory of carcinogenesis (one of several controversial theories), this aspect of photoaging could contribute to the strongly age-associated incidence of skin cancer.

Environmentally induced acceleration of the apparent aging of skin has been investigated at the cellular level, as well as clinically, with the in vitro model first described by Hayflick some 25 years ago (Hayflick, 1965; Hayflick and Moorhead, 1961). It is now well accepted that human fibroblasts have a finite, reproducible life span in culture (Hayflick, 1979), that culture life span is inversely related to donor age (Martin et al., 1970; Schneider and Mitsui, 1976), and that culture life span is decreased relative to that of cultures from age-matched control donors for fibroblasts derived from people with some disorders considered to represent premature aging (Martin et al., 1970).

To determine whether habitual exposure to the sun accelerates chronologic aging in skin-derived cells, cultures of dermal fibroblasts (Schneider and Mitsui, 1976) and epidermal keratinocytes (Gilchrest, 1980) were established from paired biopsy sites on the inner (sun-protected) and outer (sun-exposed) aspects of the upper arms of nine healthy, fair-skinned, male volunteers aged 28– 86. Volunteers had comparable lifelong annual exposure and no substantial exposure within 4 months of the biopsy. The paired cultures were maintained under identical standard conditions and serially passaged until senescence.

The cultures derived from sun-protected sites underwent more cumulative population doublings than did paired cultures derived from the sun-exposed sites, and the magnitude of the discrepancy increased with donor age and clinical severity of the photoaging

changes. Similar results were obtained with fibroblast cultures derived from different paired sites—sun-exposed and sun-protected skin removed from around the ears of older women during face-lift procedures (Gilchrest et al., 1983). The data suggest that habitual exposure to the sun does accelerate cellular aging, as judged by at least one criterion.

Photoaging and chronologic or intrinsic aging in the skin have striking similarities, but the processes can be distinguished at the electron microscopic level (Braverman and Fonferko, 1982a,b; Lavker, 1979). The ability to distinguish between them offers the hope that the effect of environmental factors other than exposure to the sun might also be differentiated from intrinsic aging, even in the absence of control tissue not environmentally exposed (a major advantage in skin), given sufficient knowledge of normal morphologic and physiologic aging changes. However, it will not be easily accomplished. In middle-aged or elderly people, even casual comparison of habitually exposed versus protected sites (e.g., face or hand versus buttock or breast) immediately suggests different aging rates, with lines of demarcation corresponding to clothing styles, rather than to anatomic compartments.

Nevertheless, the major role of environment in skin aging has only recently been accepted. That implies that overwhelming evidence will be required to convince both scientists and the public of other adverse environmental impacts on the perceived aging process.

VISION

A number of changes take place in the tissues of the eye in association with aging. Some account for a good deal of the blindness and visual loss in older people. The impact of environmental factors on these "biologic markers" of aging is only beginning to be understood. Substantial visual impairment occurs in 6% of people over 65 and in 46% of those over 85. Aging-related macular degeneration, associated with changes in the retinal epithelium, accounts for some of these cases; nonneuronal change (cataract and glaucoma) accounts for the rest.

Cataracts

Cataracts—opacities of the lenses of the eyes—are so directly

connected with aging processes that it has been suggested that everyone would develop them if people lived long enough. It is estimated that the vision of about 17 million people around the world is impaired by cataracts, and in developing countries cataract is the major cause of curable blindness. About a million Americans are affected by cataract; it is a major cause of blindness in the United States. About 60% of Americans between the ages of 65 and 74 have some signs of cataract.

Epidemiologic data show striking regional differences in the prevalence of cataracts and suggest that environmental factors play a role in its etiology (to restore sight). For example, cataract incidence is extraordinarily high in Tibet and Nepal, and a three-fold difference in prevalence of cataract has been reported among different climatic zones in northern India. Population studies have shown a striking difference between the United States and India in the age-specific prevalence of cataracts: for the age groups 52–64, 65–74, and 75–85, rates were 5%, 18%, and 46%, respectively, in the United States and 29%, 43%, and 82% in India.

Major identified risk factors related to the etiology of age-related cataract include the following:

- *Sex.* Females are at increased risk, which suggests a role for endocrine factors. Further research on this subject is needed.
- *Ultraviolet irradiation.* Geographic studies have shown that increased risk of cataracts is associated with living in areas that receive large amounts of sunlight or are at high altitudes. The high prevalences of cataract in Tibet and Nepal have suggested this association since prolonged exposure to sunlight, and hence UV irradiation (which is greater at high than at low altitudes), is present in these locations. A current hypothesis suggests that the initial reactions involve oxidative mechanisms that can act on proteins of the lens, including membrane Na^+-K^+ ATPase, a key element in regulation of salt and water distribution in tissues. Excessive lens hydration causes swelling and disruption of the cellular membranes and cellular destruction, and finally blocks light transmission through the lens. It is known that various forms of ionizing radiation can cause experimental cataracts and thus are recognized as occupational hazards that lead to cataracts.
- *Diabetes.* Biochemical changes in the lens and the fluid that bathes it cause changes in the metabolism of glucose in the

lens. In experimental "sugar" cataracts, glucose metabolism proceeds by an alternative oxidative metabolic pathway rather than a normal anaerobic series of energy-producing reactions that lead to the accumulation of sorbitol, a sugar alcohol, in the lens fibers (McLean et al., 1985). The increased sorbitol concentration produces an osmotic gradient, draws water from the aqueous humor into the lens fibers, causes the lens fibers to swell and eventually become disrupted, and finally produces opacification of the lens. The enzyme aldose reductase produces the sorbitol, and agents that inhibit it have prevented experimental cataracts (Kador et al., 1985).

Glaucoma

Glaucoma (primary open-angle glaucoma) is associated with aging. Glaucoma is characterized by loss of visual field, changes in the appearance of the optic nerve, and increased intraocular pressure (pressure higher than a given eye can tolerate). Intraocular pressure is regulated by a balancing of the rate of aqueous humor formation and the rate at which it leaves the eye, filtering through the trabecular meshwork. In glaucoma, ultrastructural factors in the meshwork slow the filtration and increase the intraocular pressure.

Epidemiologic studies have shown a sharp increase in the prevalence of glaucoma with age. A survey of available information suggests prevalence rates for glaucoma of 2–6% in predominantly white populations. Prevalence at age 70 is several times that at age 40 (U.S. National Advisory Eye Council, 1983). However, those data are derived from studies conducted under various conditions and in populations of different sizes, and they reflect detection of glaucoma in rather small numbers of patients.

Clinical observations have suggested that the prevalence of glaucoma is greater in blacks than in whites. Recent findings of a large, well-designed survey in Baltimore indicate that the overall prevalence of glaucoma among blacks is 5.8%, distributed as follows: in 1.9% of those aged 40–49, 4.7% of those 50–59, 7.4% of those 60–69, and 12% of those aged 70 and older. Data from a comparable white population are under analysis (Tielsch et al., 1986).

A morphometric study of trabecular meshwork specimens collected from normal eyes demonstrated a progressive decrease in

cellularity with aging (Alvarado et al., 1981). Comparable measurements of tissues from glaucomatous eyes indicated that the process is accelerated in glaucoma (Alvarado et al., 1984a,b), which suggests premature aging of the meshwork in glaucoma.

Diabetic Retinopathy

Diabetic retinopathy affects the central macular area of the retina—the region of greatest visual acuity—more severely than peripheral areas. Major clinical signs of retinopathy are closure of blood vessels, vessel leakage, and growth of new vessels that tend to be fragile and leaky. The resulting hemorrhages often lead to scar-tissue formation, tension on the retina, its detachment, and blindness.

Some 90% of people with insulin-dependent diabetes that has lasted 15 years show some degree of retinopathy; after 30 years, about 50% have proliferative retinal vascular changes. To the extent that diabetes can be attributed to environmental factors such as diet, diabetic retinopathy might be avoidable.

Aging-Related Macular Degeneration

Aging-related macular degeneration, formerly known as senile macular degeneration, affects the central high-acuity area of the retina and leads to severe loss of vision. The disease is a major cause of visual impairment in people over 60. About 90% of elderly people have some form of retinal degeneration. Most of them have the mild “dry” or nonexudative type, which generally progresses slowly. In the more severe “wet” form of the disease, exudative maculopathy, neovascularization occurs—abnormal new vessels grow inward from the choroid, through Bruch's membrane, and lie beneath the retinal pigment epithelium. Bleeding from the new vessels initiates processes that break down the retinal pigment epithelium, elevate the retina, and damage vision. In nonexudative maculopathy, the vessels have not broken through Bruch's membrane; however, this form can progress to exudative maculopathy. Maculopathy can be reduced by laser photocoagulation.

A recent examination of pathogenetic factors of aging-related macular degeneration indicates that risk factors include drusen, choroidal vascular disease, and vitamin C deficiency (Feeney-Burns and Ellerseick, 1985). Drusen, small yellowish bodies

observed ophthalmoscopically under the macula in Bruch's membrane, normally increase with age. Special changes in their number and appearance are noted in maculopathy. A recent electron micrographic study surveyed changes in Bruch's membrane with age (Tso, 1985). Morphologic changes in the macular region progressed from the second decade.

HEARING

Hearing impairment is a major affliction of the elderly, affecting more than one-fourth of those past 65 (Katzman and Terry, 1983). Most cases are idiopathic (often they are of genetic origin) and result from loss of sensory hair cells in the inner ear and involvement of the auditory nerve; but ototoxicity due to drug ingestion is also well recognized. The possible contribution of lifelong environmental noise pollution is unknown, although shorter-term exposure to very loud noises is well known to impair hearing permanently (World Health Organization, 1980).

Noise-induced hearing loss (NIHL) is caused by daily exposure to intense sound over a long period (months or years). Gradually, slight insult is added to slight insult until a permanent hearing loss is produced. This type of hearing loss constitutes the vast majority of hearing losses observed in the occupational setting.

Presbycusis is the deterioration in hearing associated with aging. It remains to be determined whether there is interaction between presbycusis and NIHL and whether one's sensitivity to NIHL depends on age. It has been suggested (Helmkamp et al., 1984; Spoor, 1967) that interaction between presbycusis and NIHL is not purely additive.

NERVOUS SYSTEM

Changes Associated with Aging

Aging is associated with important changes in the nervous system (Katzman and Terry, 1983), and an age-related decline in neural function might allow previously silent neurotoxic disorders to reach clinical expression (Calne et al., 1986). Clinical experience with therapeutic drugs has indicated that the elderly, especially those with metabolic abnormalities or with hepatic or renal impairment, are more susceptible to the toxic effects of xenobiotic

substances (Silverstein, 1982). However, systematic studies of the effects of chemical neurotoxicants on laboratory animals of various ages have not been undertaken.

The most intensively studied and best-documented aspects of normal human aging are changes in intellect and memory. Intellectual performance—as measured by tests of vocabulary, information retention, and comprehension—reaches a peak between the ages of 20 and 30 and, in the absence of disease, is maintained throughout adult life, at least until the mid-70s. Perceptual processing and choice reaction are slowed during aging. Learning, storage, and retrieval of information associated with short-term memory are consistently impaired in older subjects.

Motor tasks—including locomotion, handwriting, and other purposeful movements—are performed more slowly, weakly, or in an uncoordinated manner. Muscle wasting is common, strength is reduced, and tendon reflexes become difficult to elicit (Katzman and Terry, 1983). Vibration sense is progressively compromised with advancing age, touch sensation is diminished, thermal discrimination is impaired, and the pain threshold is mildly raised. Defective thermal regulation and decreased lacrimation also occur with age. Sleeping patterns are altered.

Neurobehavioral changes that accompany human aging are associated with structural or functional alterations in the central and peripheral nervous systems. Some changes—such as alterations in vascular and cardiac reflexes, galvanic skin response, potency, micturition, and pupillary response—probably result from changes in the autonomic nervous system (Katzman and Terry, 1983). Sympathetic hyperactivity is commonly present in the aged and might interfere with cognitive functioning, especially under the stress of psychologic testing. People with sympathetic hyperactivity would be expected to be more susceptible to chemical toxicants with sympathomimetic properties. Changes in cerebral blood flow, essential for the maintenance of normal brain function, might occur after the age of 80.

Cerebral cortical atrophy and ventricular enlargement have been documented in normal aging people. Some regions of the brain are more susceptible to neuronal cell loss: the locus ceruleus and substantia nigra (McGeer et al., 1977), both of which undergo maximal reduction in the third and fourth decades and decline slowly thereafter; Purkinje's cells; and putamen neurons, which decline linearly in number (Katzman and Terry, 1983). But several

cranial nuclei and the olivary nucleus maintain stable populations. The number of cerebral cortical neurons can be reduced by up to half from age 20 to age 80, and supplementary reductions and alterations occur in their dendritic arborizations and synaptic inputs. The volume of lipofuscin, a yellow, insoluble pigment, increases linearly in most neurons with increasing age, but there is no evidence that this material is cytotoxic.

Other neuronal abnormalities in aged brains include neurofibrillary tangles, neuritic plaques, and granulovacuolar bodies. Neuronal changes and cell loss result in substantial local or generalized alterations in the concentration of neurotransmitters, including dopamine, norepinephrine, serotonin, gamma-aminobutyric acid, and choline acetyltransferase, the enzyme required for the synthesis of the neurotransmitter acetylcholine (Katzman and Terry, 1983).

Morphologic age-related changes in the peripheral nervous system include a probable reduction of sensory neurons, an increase in the incidence of demyelination in spinal roots and peripheral nerves, increases in connective tissue, and a mild loss of myelinated fibers (Spencer and Ochoa, 1981). The central processes of dorsal root ganglion cells typically undergo distal dystrophic and degenerative changes. There is a slight reduction in the number of motor neurons with age (Tomlinson and Irving, 1977), and regressive changes have been reported in the terminals of motor axons. Changes in sensory and motor nerve conduction with a progressive slowing of nerve action potentials are also characteristic.

Induced Disorders and Diseases

The neurologic effects of aging and of chemical substances overlap considerably. This overlap might indicate only that the nervous system has a limited repertoire of biologic expression or that the mechanisms involved in neural aging can be traced to toxic effects of circulating metabolites derived from both endogenous and exogenous sources.

It is generally believed that the clinical expression of disordered neural function resulting from aging becomes evident only after the considerable structural and functional redundancy of the nervous system has been overcome. For example, a maintained parkinsonian state appears only after a considerable loss of neurons in the substantia nigra, and it can occur as a consequence

of aging. Some people might be at special risk for neurotoxic disorders because of genetic characteristics (e.g., slow acetylators prompting isoniazid toxicity), abnormal metabolic states (e.g., undernutrition), leaky blood-brain regulatory interfaces (e.g., liver compromise), or aging (e.g., poor renal clearance). The elderly are generally more susceptible than the young to the potential neurotoxic side effects of therapeutic drugs and other chemical substances.

Specific environmental influences (such as effects of exposure to chemical toxicants and environmental toxins) on aging have been proposed as a general mechanism for the cause of major degenerative diseases of the elderly that affect intellectual and motor function (Calne et al., 1986). Presenile dementia of the Alzheimer type, Parkinson's disease, and amyotrophic lateral sclerosis are proposed to derive from environmental subclinical damage to specific regions of the central nervous system that are particularly vulnerable to age-related neuronal attrition. For parkinsonism, the hypothesis is being tested in people with subclinical damage to the substantia nigra after exposure to MPTP (Langston, 1985). Because nigral neurons decline with age, it is likely that characteristic features of the disease will evolve in later life.

For amyotrophic lateral sclerosis and presenile dementia, the spotlight is on the indigenous population of Guam, which is peculiarly susceptible to these conditions as well as to parkinsonism (Spencer et al., 1987). Epidemiologists have found that exposure to the environment of Guam for a minimum of the first 20 years of life is sufficient to establish the conditions necessary to develop amyotrophic lateral sclerosis or parkinsonism-dementia decades later (Garruto et al., 1980). Suspect etiologic agents are the cycad plant *(Cycas circinalis)* (Spencer et al., 1987) and aluminum (Perl et al., 1982).

Neurotoxicants

Among the environmental pollutants with neurotoxic potential, lead and mercury each occupy a prominent position, although the number of people in North America with overt neurotoxic disorders attributable to these sources is probably small. In addition, numerous plants and animals secrete or contain potent toxins, of which many disturb nerve conduction and one, ciguatoxin, is a major cause of acute neurotoxicity in the Pacific among those

who eat contaminated fish (Kaplan, 1980). Other neurotoxins (e.g., α-bungarotoxin and α-latrotoxin) affect synaptic transmission. Both types can produce acute, life-threatening conditions. Some of the agents find their way into food and water consumed by humans. Some chemicals with experimentally proven neurotoxic potential in animals are used as food additives (e.g., monosodium glutamate), flavors and fragrances (e.g., 2,6-dinitro-3-methoxy-4-*tert*-butyl toluene), and antiseborrheic agents (e.g., zinc pyridinethione), but no cases of human neurotoxic disease from these sources have been reported.

In developing countries, biologic toxins (e.g., *Clostridium botulinum, C. tetani,* and *Corynebacterium diphtheriae*), neurotoxic agents naturally present in food (e.g., cassava, cycad, and *Lathyrus* spp.) or as contaminants (e.g., ergot and aflatoxin), and pesticides probably account for a large proportion of human neurotoxic disorders. Pesticide intoxication is a worldwide problem. Uncontrolled cholinergic crises, sometimes leading to death, are common in some regions among agricultural and pesticide workers (Bull, 1982), and long-lasting changes in the electroencephalograms and behavior of surviving persons have been recorded (Duffy et al., 1979). Other pesticides contain tremor- and seizure-inducing organochlorines or synthetic pyrethroids that perturb neurotransmission (Narahashi, 1984; Taylor et al., 1979). The worldwide problem of substance abuse—particularly of ethanol, hallucinogens, narcotics, central nervous system stimulants, solvents, and nitrous oxide—leads to various types of short- or long-lasting neurologic dysfunction.

Many other substances encountered in the workplace (e.g., solvents, monomers, and catalysts) have been associated with neurologic illnesses ranging from polyneuropathy to organic brain syndrome. This spectrum of disorders was observed in workers exposed for only a few weeks to one particularly potent industrial neurotoxicant, Lucel-7 (2-*tert*-butylazo-2-hydroxy-5-methylhexane) (Spencer et al., 1985).

Dementia, delirium, and depression can all result from exposure to pharmaceuticals. Learoyd (1972) found that 16% of 236 patients over 65 who were hospitalized for behavioral disturbances had disorders directly attributable to the effects of psychoactive drugs. In a recent study of 107 unselected outpatients referred for evaluation of global mental impairment (memory loss, confusion, slow thought, inability to care, and self-neglect), Larson et al. (1984) found that 15 patients had potentially reversible dementias,

or chronic progressive deterioration of higher intellectual function. The most common cause was medication.

Side effects of single drugs that were potential causes of dementia included confusion caused by amantidine, insulin-induced hypoglycemia, and haloperidol-induced oversedation and parkinsonism. Several drug combinations were implicated: clorazepate and lorazepam; meprobamate, protriptyline, and thioridazine; and reserpine, diazepam, and meprobamate.

Dementia can be reversible, particularly when caused by drugs, heavy metals, or industrial chemicals (Cummings et al., 1980). Drugs that have been reported to cause dementia can be grouped into four main categories: psychotropic medications, such as phenothiazines, butyrophenones, benzodiazepines, tricyclic antidepressants, and lithium carbonate; anticonvulsants, such as phenytoin, mephenytoin, and carbamazepine; antihypertensive agents, such as clonidine, methyldopa, and propranolol; and anticholinergic compounds, such as atropine and antihistamines. Heavy metals —including lead, mercury, thallium, and arsenic—can cause intellectual impairments that are reversible by chelation or reduction of exposure.

Even though proprietary bromide preparations are much less available than in the past, bromide intoxication should be considered as another insidious cause of dementia (Raskind et al., 1978). It has been reported that the concentration of aluminum in the brains of patients who died with senile dementia of Alzheimer's type is 10–30 times the normal concentration (Crapper et al., 1976). Later studies have localized aluminum to cells with neurofibrillary tangles (Perl and Brody, 1980), but its role in the pathogenesis of the disease remains controversial (Glenner, 1982). Long-term exposure to industrial agents —including trichloroethylene, toluene, carbon disulfide, organophosphates, and carbon monoxide—has resulted in mental status changes that reversed with elimination of the causative agents (Cummings et al., 1980).

The term delirium applies to organic brain syndromes characterized by the rapid onset of cognitive dysfunction involving fluctuating impairments of attention, memory, and orientation. Common symptoms include insomnia or reduction in wakefulness, such perceptual disturbances as illusions and hallucinations, and changes in psychomotor activity, particularly agitation. Elderly patients, particularly those already suffering from dementia, are most susceptible to developing drug-induced delirium (Barnes

and Raskind, 1980). Levodopa, amantidine, corticosteroids, and many drugs with anticholinergic properties are often responsible. Barbiturates and other sedative hypnotic agents can also cause paradoxic agitated delirium in susceptible patients.

Depression can be a complication of drug therapy. Antihypertensive agents —such as reserpine, methyldopa, and clonidine— have been reported to cause depressive symptoms, but a greater incidence seems to be associated with beta-blockers than with those centrally acting agents. There is ample anecdotal evidence of patients with no prior psychiatric illness who experience malaise, dysphoria, or outright clinical depression when starting treatment with beta-adrenergic antagonists, and central nervous system side effects from propranolol range in frequency from 1% to over 70% (Paykel et al., 1982). Reported symptoms include depression, drowsiness, sleep disorders, and hallucinations.

Furthermore, the use of tricyclic antidepressants has been found to be significantly higher in patients taking beta-blockers (23% over 2 years) than in patients taking hydralazine or hypoglycemics (both 15%) or methyldopa or reserpine (both 10%). However, the magnitude of this association between beta-blockers and treatment for depression was found to decline with advancing age (Avorn, 1986). Proposed explanations were diminution in receptor sensitivity with age and failure of physicians to appreciate the dysphoria or other central nervous system side effects as abnormal in an older patient. The mechanism of the central effect of beta-blockers could be interference with nonadrenergic neurotransmitter function in the brain, a pathway that is thought to play a causal role in some cases of depression.

In general, the signs and symptoms of drug-induced neurologic disorders are practically indistinguishable from those seen in nondrug-induced disorders, but are usually reversible if diagnosed early enough (Lane and Routledge, 1983). Neurotoxicity commonly accompanies prolonged therapeutic treatment with anticonvulsants, anticholinergics, neuroleptics, antineoplastics, and antiparkinsonism drugs. In addition, a recently recognized iatrogenic neurotoxicity is the sensory neuropathy syndrome associated with pyridoxine megavitamin therapy (Schaumburg et al., 1983), which has been prescribed for the treatment of premenstrual tension.

The incidence of subclinical neurologic and behavioral disorders associated with chemical substances is unknown, but is

believed by some to be large. Examples include the unresolved controversies about childhood cognitive impairment from environmental lead contamination and the neurobehavioral effects attributed to prolonged occupational exposure to a variety of industrial solvents.

RESPIRATORY SYSTEM

Lung growth and development continue into the second decade of life, and then pulmonary function begins to decline. The decline is most easily measured with tests of forced expiration. Many prospective epidemiologic studies indicate that the forced expiratory volume in 1 second (FEV_1) decreases continuously with age, even in healthy nonsmokers. The rate of loss is greater in older than in younger people (Beaty et al., 1984; Burrows et al., 1986; Fletcher, 1976; Higgins et al., 1982). Smokers lose pulmonary function much faster than nonsmokers, but if they stop smoking, their rate of decline reverts to the rate observed in nonsmokers (Fletcher, 1976).

Although an understanding of the association between aging and environmental insults to the lungs is limited, two features are noteworthy because of pathophysiologic correlations. First, when the structure and function of small airways are measured, age and smoking are found to have important effects. Even in young, presumably healthy smokers, evidence of inflammatory responses in peripheral airways is striking (Niewoehner et al., 1974). Small-airway dysfunction increases with age and can be observed in smokers of all ages (Enjeti et al., 1978). Those observations have led to the recognition of the importance of peripheral lung structure and function in the evolution of lung aging or disease and to the focus for the last 15 years on studies of peripheral lung function in the evaluation of environmental exposures (Macklem, 1972).

The second important feature of lung function is airway reactivity. Acute reactions of the airways are typically increased in asthmatic subjects, but might be increased in normal subjects who smoke (Gerrard et al., 1980; Mullen et al., 1986), after viral infections, and after exposure to oxidants, such as ozone (Boushey et al., 1980). Airway reactivity can be measured in the laboratory with controlled administration of bronchoconstricting agents. A number of studies now point to the potential importance of increased

airway reactivity as a risk factor for accelerated loss of function with age (Barter and Campbell, 1976; Orie, 1960; Vollmer, 1985). The evidence implicating ambient concentrations of air pollutants in the decline of lung function with age is controversial (U.S. EPA, 1986). However, the potential impact of environmental exposures, either outdoor or indoor, on susceptible people is real.

Not only is there clear epidemiologic evidence that age and environmental factors, such as smoking, are associated with loss of lung function, equally clear is an important correlation between lung dysfunction and mortality from all causes (pulmonary and nonpulmonary). From epidemiologic studies in Tecumseh (Higgins and Keller, 1970), Framingham (Ashley et al., 1975), and Baltimore (Beaty et al., 1982; Menkes et al., 1985), a consistent, strong relationship between lung function and mortality has been reported. It cannot be accounted for by smoking habits and reflects (to a small extent) deaths from chronic lung disease or lung cancer (Skillrud, 1986).

Although the basis of the intriguing association is not known, two explanations are attractive. First, because the lung is normally an interface between the body and the environment, increased exposure to environmental toxins or increased susceptibility of the host leads to disturbances of the lungs, as well as of other systems of the body. Second, disturbances of function in organ systems other than the lungs might lead to abnormalities in otherwise normal lungs. Both explanations are suggest the importance of lung function in estimating environmental exposure and in assessing individual susceptibility to nonpulmonary, as well as pulmonary, aging and disease.

CARDIOVASCULAR SYSTEM

Some characteristic age-related changes in the cardiovascular system are stenotic coronary vascular disease due to atherosclerosis, stiffening of the large arteries, an increase in systolic blood pressure, and mild cardiac hypertrophy and concomitant reduced cardiac filling rate with unchanged cardiac filling volume and resting cardiac output (Lakatta, 1985a,b, 1986).

More subtle manifestations of aging can be detected with the imposition of a stress, such as exercise. Age-related changes in the hemodynamic response to vigorous exercise include a diminution in the increment in heart rate, increase in heart size (which is

normal at rest) both at the end of the filling period and at the end of the contraction period, and reduction in the increment in ejection fraction (the proportion of the filling volume pumped with each contraction of the heart) (Rodeheffer et al., 1984).

These changes can be explained by an age-related diminution in the response of the cardiovascular system to catecholamines produced by the activation of the sympathetic nervous system (which occurs during exercise). Considerable evidence from both experimental animals and humans indicated that the sensitivity of cardiac and vascular tissue to β-adrenergic agonists' autonomic modulation declines with age (Bertel et al., 1980; Conway et al., 1971; Fleisch, 1981; Kuramoto et al., 1978; Vestal et al., 1979; Yin et al., 1979, 1981).

Despite a substantial body of information on the effects of aging on cardiovascular physiology, the extent to which the aged might be particularly vulnerable to the toxic effects of drugs, chemicals, and other environmental agents has received scant attention. The possibility of a difference in the response of the aged myocardium to cardiac glycosides, such as ouabain and digoxin, has been investigated in animals and humans (Algeo et al., 1983). Developed tension and maximal rate of tension development in isometric trabeculae carneae were approximately 4 times greater in young than in aged Wistar rat myocardium (Gerstenblith et al., 1979). There was no age-dependent difference in ouabain-induced Na^+-K^+-ATPase inhibition, which is a postulated mechanism of action for ouabain and other digitalis preparations. In contrast, activity of the Na^+-K^+ ATPase was 50% less in aged Fischer 344 rats than in younger rats, and the toxicity of ouabain was inversely related to enzyme activity (Baskin et al., 1977).

Ouabain also inhibited enzyme activity more in older than in younger rats. In guinea pigs, however, the median lethal dose of ouabain infused into adult and aged (up to about 5–6.5 years old) guinea pigs did not differ (Wollenberger et al., 1953).

In elderly humans, an age difference in the inotropic response to digitalis was not demonstrated (Cokkinos et al., 1980). The inotropic response, as measured by systolic intervals, to deslanoside (1.2 mg intravenously) was similar in a group of 20 healthy males and females (mean age 34.3 years) and a group of 20 healthy older subjects (mean age 65.3 years). The clinical effects of acetyldigoxin in congestive heart failure and digoxin in atrial fibrillation do not differ with age (Aravanis, 1969; Chamberlain et al., 1970). Thus,

apart from the increase in plasma digoxin due to diminished renal excretion in the elderly, there is little evidence to support the widely held notion that intrinsic myocardial sensitivity to digitalis is increased in old age.

Age-related data on antiarrhythmic agents are even less extensive than those available on cardiac glycosides; they generally indicate no significant increase in sensitivity or toxicity in the absence of abnormal conduction. A recent clinical study demonstrated altered sensitivity to verapamil, a calcium-channel antagonist. Age differences in pharmacokinetics resulted in higher plasma concentrations in elderly than in young patients (Abernethy et al., 1986).

Doxorubicin (adriamycin), an anthracycline cancer chemotherapeutic agent, appears to have important age-related cardiac toxicity. A major problem with administration of doxorubicin for therapeutic purposes is the development of often irreversible and often fatal congestive heart failure. The effect seems to be dose-related, and cumulative doses greater than 550 mg/m^2 result in a marked increase in the incidence of heart failure (Lefrak et al., 1973). If more sensitive measures of cardiac function are used such as systolic intervals, cardiac impairment after doxorubicin therapy (greater than 400 mg/m^2) is detectable in approximately 15% of patients (Dresdale et al., 1983). Degenerative changes in cardiac histology occur almost universally at doses greater than 240 mg/m^2 (Bristow et al., 1978). Apart from cumulative dose, old age was the major risk factor observed in a retrospective survey of 4,000 patients (Von Hoff et al., 1979).

Others have also noted that aging is a risk factor for development of cardiotoxicity (Bristow et al., 1978; Dresdale et al., 1983), but not because of a higher incidence of coronary heart disease in older patients (Von Hoff et al., 1979). The mechanism of cardiotoxicity of doxorubicin is not known, but could be the production of free radicals (Olson et al., 1981; Unverferth et al., 1982). Pathways of free-radical detoxification are depressed in some tissues of senescent laboratory animals (Stohs et al., 1982), so myocardial free-radical scavenging might be impaired in elderly patients.

The clinical observations related to doxorubicin suggest that other chemicals and environmental agents that produce free radicals might be associated with myocardial damage and that the effects might increase with age. Surprisingly, data on that point

are not available; indeed, it appears that the impact of age on cardiovascular toxicity has been virtually ignored by toxicologists and epidemiologists.

RENAL SYSTEM

Chronic nephropathy involving glomerular sclerosis, mesangial cell injury, and mesangial matrix overproduction is commonly found in rats at advanced ages (Coleman et al., 1977; Durand et al., 1964). Similar progressive lesions are observed in young rats after surgical reduction of kidney mass (Chanutin and Ferris, 1932; Purkerson et al., 1976; Shimamura and Morrison, 1975) and in humans, usually at advanced ages, after disease-induced kidney damage when the initial disease process is no longer active (Brenner et al., 1982). Decreasing the protein content of the diet of rats has been found to retard the development of the nephropathy that occurs during normal aging (Maeda et al., 1985) and that follows surgical reduction of kidney mass (Hostetter et al., 1981; Laouari et al., 1983; Moise and Smith, 1927).

Moreover, there is evidence that reducing the protein intake of humans slows the progression of chronic renal failure to end-stage disease (Mitch, 1984). Brenner et al. (1982) suggested that a decrease in dietary protein acts by preventing glomerular hyperperfusion and hyperfiltration, which they thought responsible for the progression of the lesions and for the eventual loss of renal function.

Iwasaki et al. (1986) recently reported that the development of kidney lesions in male Fischer 344 rats during normal aging can be retarded by using soy protein as the source of dietary protein without reducing protein intake. That finding is important in two respects: for animal models for the study of aging and in treatment of chronic renal failure in humans.

The male Fischer 344 rat has been a major animal model (National Research Council, 1981b) for the study of aging, because it is genetically homogeneous and because it does not develop the obesity that occurs with advancing age in many rat strains. However, a major problem with the strain, as with most other rat strains, has been renal failure with advancing age, which precludes the study of normal aging processes in some of the rats by the age of 18 months and in many after the age of 24 months. Diets with soy protein as the sole protein source might, to a great extent,

circumvent the problem and thus facilitate full life-span studies with the Fischer 344 rat.

Although available data indicate that restricting dietary protein in patients with chronic renal failure delays the further loss of renal function and lengthens the time before they need dialysis or transplantation, such treatment has the risk of protein malnutrition, as well as mineral and vitamin depletion (Mitch, 1984). The proper selection of the dietary protein source might yield a treatment for chronic renal failure as effective as protein restriction but without its risks.

IMMUNE SYSTEM

One of the most important body defenses is the immune system. Environmental influences on the immune system include the effects of psychologic stress (including bereavement), nutrition, environmental temperature, housing, light, noise, and chemicals. Some environmental influences on immune function affect life span and therefore presumably affect susceptibility to disease or the aging processes themselves.

Of the environmental factors, nutrition has a most dramatic effect on both immunity and life span in rodents. Reducing caloric intake of mice and rats by approximately 50% of their ad libitum intake inhibits the age-associated decline in immune competence, reduces the incidence of many diseases (including cancer), and extends life span. Undernutrition has been shown to increase the life span of a number of short-lived strains of mice (reviewed in Good et al., 1980). Whether a similar nutritional regimen would influence the life span of higher organisms, including humans, is unknown.

Clear evidence exists that the barrier between an organism and its environment is altered with age (for a review see Weksler, 1986). The immune function of the skin and the mucosal lining of the respiratory and gastrointestinal tracts change with age, although such change does not always parallel the changes in systemic immunity.

Far more is known about the changes in systemic immunity that accompany aging in rodents and humans. The most striking anatomic change is the involution of the thymus gland that begins at sexual maturity and is complete by midlife (45–50 years in humans), and that results in the loss of two thymic functions. The

first thymic function that declines with age is the capacity to effect the maturation of T-cell precursors that migrate to the gland from the bone marrow. The second is the activity of thymic hormone in the serum, which begins to decline soon after sexual maturity. Thymic hormone activity in serum is undetectable in humans after midlife.

The thymus, the source of mature T lymphocytes, plays a central role in cell-mediated immune responses and the regulation of the immune response. Not surprisingly, therefore, immune senescence is characterized by a loss of thymus-dependent functions required for both cellular immunity and the regulation of humoral immunity. Inasmuch as the response to many pathogens — including viruses and fungi, as well as neoplastic cells and some environmental agents—depends on cell-mediated immunity, the susceptibility of the aged to diseases induced by these agents is increased. The striking increase in the morbidity and mortality associated with influenza in elderly people is a common clinical consequence of immune senescence.

In addition to the loss of cell-mediated immunity with age, the loss of thymic function leads to the dysregulation of immune reactions. The striking increases in the frequency of autoantibodies and in the production of monoclonal immunoglobulins with age reflect this fact. Impaired suppressor-cell activity in old age is thought to contribute to the increases in autoantibodies and monoclonal proteins with age. Those autoimmune reactions might be exacerbated when elderly people take such drugs as procainamide, α-methyldopa, or estrogens, which themselves stimulate the production of autoantibodies. When autoantibodies react with autoantigens, they form immune complexes. Circulating immune complexes can contribute to vascular injury and thereby to the increasing severity of atherosclerosis in the elderly.

Progress has been made in understanding the cellular basis of lymphocyte function that is attributable to a loss of the capacity of T lymphocytes to divide. The evidence suggests that the cellular basis of immune senescence is similar to what Hayflick suggested 20 years ago (Hayflick, 1965) in cultured fibroblasts—the loss of replicative capacity. Any environmental agent that compromised the capacity of cells to divide would thus be likely to depress immune competence and accelerate immune senescence.

SEXUALITY

The fear of losing sexual ability or physical attractiveness can be a source of great anxiety for many people as they grow older. Men typically are afraid of sexual impotence; women fear the loss of physical attractiveness and desirability. A number of gradual and fairly predictable physiologic changes do occur with aging, but these changes do not preclude active and satisfying sexual functioning into old age.

Most of the sexual changes in older women result from the menopausal decline of female hormones, especially estrogen. Environmental agents, such as ionizing radiation, pharmaceuticals, and cigarette smoking, have been shown to alter the age of menopause (i.e., ovarian failure) (Chapman, 1983; Mattison, 1985; Mattison and Ross, 1983). However, 60% of all women do not experience remarkable physical or emotional symptoms associated with menopause, and of those who do, most have only minimal to moderate physical problems, including headaches and neckaches, hot flashes, fatigue, and feelings of emotional instability.

Physically healthy men do not lose their capacity to have erections and ejaculations as they age, although changes do occur. With age, men ordinarily begin to take longer to obtain an erection and to reach orgasm than when they were younger.

Drugs, taken by prescription or otherwise, can aggravate these effects and cause other sexual problems. Some interfere with the autonomic nervous system, which is involved in normal sexual response. Others affect mood and alertness or change the production or action of sex hormones. In a study reported in 1983, 25% of sexual problems in men were either caused or complicated by medications (Butler and Lewis, 1986). Although less is known about drugs and female sexuality, drugs affecting men can be assumed to affect women as well (Butler and Lewis, 1986).

Tranquilizers, antidepressants, and some antihypertensive agents have all been implicated in erectile impairment in men. The effects of these drugs on women is less well understood. The corticosteroids taken for arthritis can produce temporary impotence. Analgesics can reduce sensitivity and therefore affect male sexual capacity. Aspirin taken over long periods reduces fertility. Cimetidine (for treatment of ulcers), one of the most widely sold medicines in the United States, can cause impotence. Alcohol in more than small amounts reduces potency in males and orgasmic

ability in females. Even nicotine can be a factor in impotence. Although a number of gradual and fairly predictable changes in sexual function occur with aging, they are often confounded by the effects of environmental agents.

ROLE OF ENVIRONMENT IN BONE METABOLISM AND VITAMIN D NUTRITION

One of the major problems associated with aging is the loss of bone mass. It is estimated that upwards of 10 million elderly Americans suffer from marked reduction in bone mass that compromises the architectural integrity of the skeleton and puts them at substantial risk of breaking bones. The magnitude of this public-health problem is evident in the estimated 200,000 hip fractures that occur each year. It has been estimated that $6 billion is spent each year for the acute care of people with age-related fractures (Cummings et al., 1985).

Bone loss in the elderly has many causes; among them are inadequate vitamin D and calcium absorption (influenced by estrogen concentration). Although it is well documented in Great Britain (a country that does not routinely fortify foods with vitamin D) that over 40% of males and 30% of females with hip fractures are deficient in vitamin D (Aaron et al., 1974; Chalmers et al., 1967), it has been assumed that vitamin D deficiency is not an important health problem in the United States because foods are fortified with vitamin D. An epidemiologic survey in the Southwest has revealed that over 60% of the free-living elderly subjects were obtaining less than 25% of the RDA of vitamin D from their diets (Omdahl et al., 1982). In two other studies, about 30% of elderly patients with hip fractures had evidence of vitamin D deficiency (Doppelt et al., 1983; Sokoloff, 1978).

One of the primary causes of poor vitamin D nutrition in the elderly in the United States is a decrease in or complete abstinence from consumption of milk and milk products. The decrease is related to the common misconception among the elderly that they no longer need to drink milk because milk is important only for maintaining a healthy skeleton in growing children, and to gastrointestinal discomfort caused by lack of lactase, which is responsible for hydrolyzing the lactose in milk. Very few foods naturally contain vitamin D (these include fish-liver oil, eggs, liver, and milk) or are fortified with vitamin D (milk, some cereals, and

in some countries, margarine). One quart of milk contains 400 international units (10 g) of vitamin D, which is the RDA (Holick, 1986).

If an elderly person does not consume milk or other foods that contain vitamin D or take a vitamin D supplement, it is essential for that person to sunbathe to generate enough vitamin D_3 to maintain a healthy skeleton. However, because of the increased awareness that exposure to sunlight can cause skin cancer and dry and wrinkled skin, the elderly are often advised to cover their skin with clothing or a sunscreen before going outdoors. Those measures prevent not only the damaging effect of solar irradiation, but also the beneficial effect—the production of vitamin D_3 in the skin (MacLaughlin and Holick, 1985).

7

Model Systems for the Evaluation of Toxic Agents Affecting Aging or Age-Related Diseases

The development of model systems in the field of aging is at about the same stage today as the development of model systems to detect potentially mutagenic environmental chemicals was in 1970. Screening tests had shown that potentially mutagenic chemicals belonged to a wide variety of chemical classes, for example, foods, drugs, cosmetics, agricultural chemicals, and household chemicals.

In the first phase of the development of short-term screening tests, appropriate model systems were used to obtain information on the various mechanisms that produce genetic lesions and to identify the types of genotoxic agents that would produce gene mutations, chromosomal aberrations, and aneuploidy. Those models were almost exclusively in vitro assays that used organisms ranging from bacteria to mammalian cells in culture.

The second phase was the identification of mammalian models that could be used to evaluate chemicals that had positive results in in vitro tests to determine the effects of these chemicals on somatic cells and germ cells. The later tests were selected to provide a comprehensive screen in the mammal that could generate a data base suitable for predicting human response qualitatively and quantitatively.

The development of short-term tests for mutagenicity provides

a useful example for the development of appropriate model systems to identify environmental chemicals that affect aging. The procedure in using model systems to evaluate the effects of environmental chemicals on aging is first, to identify short-term tests that can be used to screen environmental chemicals for their potential to affect aging processes or age-associated diseases; second, to screen chemicals; and third, to test those chemicals that had positive results in short-term tests in mammalian model systems to develop a data base for predicting human responses.

CONSIDERATIONS IN CHOOSING AND DESIGNING MODEL SYSTEMS

The general lack of information about the fundamental nature of aging processes poses problems for risk assessment of potential environmental agents that promote aging. In the absence of reliable information, a prudent course might be to use multiple model systems. The considerations in choosing model systems for assessing relationships between environmental agents and aging or age-related diseases include:

- Length of life or of assay.
- Previous use of the model in the study of aging and toxicology.
- Knowledge of and ability to control for adventitious microorganisms.
- Knowledge of genetic characteristics and suitability for genetic analysis.
- Capacity to maintain defined environmental conditions.
- Knowledge of pathologic changes associated with aging.
- Ready availability of the cells or organisms.
- Economic feasibility.
- Widespread use in other biologic disciplines.
- Relevance to aspects of human aging.

Life span is by far the most widely used marker in assessing the effectiveness of experimental interventions into the aging processes. If the end point is longevity, life-table data are required, including life expectancy at birth and life span of the animal model to be used. For many strains of mice and rats and for many invertebrate species, sound life-table data are available. Species with short life spans are distinctly advantageous for such uses. A short

life span enables the investigator to study the animals longitudinally throughout their lives under well-defined conditions and to analyze the data with the aim of undertaking further studies within the time frame of the investigator's scientific "life span." It must be emphasized, however, that age-associated changes might occur in a long-lived species like humans that do not occur in short-lived species. Obviously, when such changes are to be studied in an animal model, the time required for the changes to develop must be considered in relation to the animal's life span.

Many invertebrates have life spans of only a few days. Such organisms might be very useful in the early stages of a comprehensive toxicity-testing regimen. If the assay involves measures other than life span, it should also be of short duration. Fast assays cost less than slow ones, yield results rapidly, and make it possible to assay many compounds in a small space and a short time.

The importance of keeping a model free of infectious diseases is well illustrated by the reports of Paget and Lemon (1965), who compared the longevity characteristics of conventionally maintained Wistar rats with those of Wistar rats kept specific-pathogen-free in a barrier facility. Both the median length of life and the life span of the specific-pathogen-free rats were markedly greater. The data suggest that infectious disease might distort the assessment of the aging processes and thus compromise the value of the model.

The genetic characteristics of the animal model should be known and the genotype should be stable to ensure reproducibility and to ease interpretation in aging studies. An example of the problems that can be encountered otherwise is illustrated by the use of the popular "outbred" strains of rats (e.g., the Sprague-Dawley and Wistar strains) for aging research. These strains are maintained by randomly (or not so randomly) mating members of the stock; a procedure likely to result in each supplier having a stock with genetic characteristics different from those of other suppliers. The genetic heterogeneity and the investigator's lack of awareness of its existence might result in erroneous interpretations, for instance, if data are obtained on young rats from one supplier and old rats from a different supplier.

Many invertebrate species have been used extensively in sophisticated genetic analyses involving both classical and molecular genetics. For example, the metazoan organism with the best understood genetics is *Drosophila melanogaster*. The extensive differences in life expectancy and life span reported in different

studies on *D. melanogaster* might arise in part from genetic drift during laboratory propagation. Genetic drift can be avoided by frequent referral to a common source or by maintenance of stocks in a nongrowing state. The availability of a common reference strain that can survive indefinitely while frozen, which eliminates genetic drift, and its sophisticated genetics make *Caenorhabditis elegans* a system of choice also.

Riley (1981b) demonstrated that it is important to define and control all environmental conditions. He found that over 65% of conventionally housed female C3H/HeJ mice had mammary tumors at the age of 400 days, whereas fewer than 10% of the mice protected from the noise, odors, and other stressors common to conventional animal facilities had these tumors at the same age. Riley related that finding to the difference in plasma corticosterone concentrations, which were 150–500 ng/ml in the conventionally housed mice and 0–35 ng/ml in the mice housed in the protected environment.

A major advantage of invertebrate organisms is their ability to grow under completely defined environmental conditions. Moreover, the fungi and *C. elegans* can even be grown in chemically defined media, albeit with some alteration in maximal growth kinetics and other life-history traits. This capability can simplify nutritional studies on aging.

The use of cell, tissue, and organoid cultures as model systems for the investigation of the aging effects of chemical, physical, and nutritional agents on somatic cells has a number of attractive features. Tissue-culture studies can simplify interpretation of the results of in vivo studies by avoiding such variables as the effects of the neural, endocrine, and immune systems and the nutritional, microbial, and pathologic status of the host animal.

Knowledge of the pathologic changes that occur with age in an animal model is essential for both the design and the interpretation of aging studies. Published data on age-related pathology are available for some, but not all, animal models. In addition, the pathologic causes of senescent death in most invertebrates have not been well explored.

The immediate availability of a source of aged animals, maintained in carefully specified environments, would simplify many studies. The lack of availability of aged animals of short-lived

strains does not present a serious problem, because in many regards it is preferable for the investigator to be in control of the animal's environment over its whole life.

Such considerations are usually of relatively minor importance in invertebrates. Many species are readily available from a variety of sources, including stock centers and individual laboratories (see Appendix A). Many of these organisms can be shipped by regular mail without special precautions, and several species, including fungi and *C. elegans,* can be stored indefinitely in the laboratory without passage.

An advantage of the invertebrates is their relatively low cost. For example, a complete life table can be constructed from a population of 100 nematodes for a cost of about $50, including overhead, technician time, and data analysis. A comparable study using mice, however, costs at legist $10,000, and about twice that for using rats. Such cost considerations are a major force in the development of biologic markers of aging other than life span.

All strains and species mentioned here are widely used in other biologic disciplines. In particular, *Neurospora crassa, C. elegans,* and *D. melanogaster* are among the most widely studied metazoan organisms. The use of widely studied organisms is an important consideration that was covered in detail in a previous report of the National Research Council (1985).

For a toxicity-test system to be truly valuable, it must closely mimic the toxic response typical of an aging human population or must represent a relevant end point of human aging or an age-related disease. At our current poor level of understanding of aging, it is impossible to make completely informed decisions about the validity of model systems. Many fundamental physiologic and molecular processes in humans are also present in many invertebrates and other vertebrates, and there is no a priori reason to expect aging processes to be different. Each model system must be approached on its own merits, and validity assessment must be based on background information on the disease state, the model system, and the particular assay under analysis.

EXAMPLES OF MODEL SYSTEMS

In Vitro Models

The ability to maintain and grow cells and tissues outside the

body has progressed to the point where the effects of environmental agents on living cells can be studied in vitro. For the purposes of screening environmental agents, the use of such assays can result in substantial economies and efficiencies—particularly important when alternative studies require aged animals of several long-lived species or large numbers of dose-response and drug-interaction experiments. Stock cells and, in some cases, tissue explants can be cryobiologically stored in large amounts. This permits repeated assays with comparable materials and the sharing of common stock materials by numerous laboratories. Moreover, such stocks can be used to investigate cell-cell interactions, such as metabolic cooperation and metabolic transformation. Finally, tissue-culture approaches can substantially reduce the numbers of animals required for experimentation. Such methods cannot, however, be expected to eliminate the need for experimentation with intact animals.

There are three general categories of methods: organoid cultures, tissue explants, and cell culture. Organoid cultures involve the short-term maintenance of viable intact segments of tissue, for example, the full thickness of a segment of aorta. In tissue explants, the early migration and proliferation of epithelioid and fibroblastoid cell types can be observed. Cell cultures are of three general types:

- Primary clones and cultures, that is, proliferating colonies and mass cultures of cells taken directly from the animal, usually after enzymatic dispersion of biopsied tissue.
- Established, serially passaged cultures with relatively reproducible cycles of growth in early phases, but with limited replicative life span, and with a genetic makeup reflecting that of the donor animal.
- "Transformed" cell cultures with indefinite replicative potential and generally with altered genetic makeup.

Each of the materials described could prove useful for studies of the effects of environmental agents on aging. One general approach would be to explore the toxic effect of an agent as a function of donor age so as to detect unusual susceptibilities of the cells and tissue of aged subjects. Another general approach would be to use the tissue-culture methods after in vivo treatments. If a set of behaviors or phenotypes were observed with tissue from

young, treated subjects that proved to be comparable to that observed with untreated tissue from old animals, an effect of the in vivo treatments on aging processes could be inferred.

An entirely different experimental paradigm could be based on the hypothesis that established cultures with finite replicative life span recapitulate the natural history of comparable cell types in vivo in aging animals—the well-known "in vitro model of cellular aging" first developed by Hayflick and Moorhead (1961). The appropriateness of such models for the study of aging is controversial, but considerable evidence supports the proposition that the attenuation of growth observed in vitro corresponds to events occurring in vivo.

Of special interest would be the evaluation of agents that exhibit unusual toxicity in putative stem cells or that accelerate the terminal differentiation of such stem cells, because an excessive depletion of stem cells might seriously compromise the regenerative potential of tissues in aging subjects. In such studies, it will be important to investigate a variety of cell types. Most research in this field has concentrated on the in vitro aging of cultures of fibroblastoid cells established from the fetal lung or from the dermis of individual subjects of various ages. The precise cell types of origin of such cultures are not clear. Thus, it will be difficult to compare age-related changes in vivo with those observed in vitro.

Considerable progress has been made in the culture of other cell types, including epidermal keratinocytes, epidermal melanocytes, lenticular epithelial cells, renal epithelial cells, chondrocytes, arterial and venous endothelial cells, vascular smooth muscle cells, skeletal muscle satellite cells and myoblasts, erythroid stem cells, myeloid stem cells, T and B lymphocytes, glial cells, and retinal epithelial cells. Much of this progress has been associated with the improved characterizations of optimal growth media, especially of subsets of growth factors. In some instances, growth in chemically defined or nearly defined media has been achieved.

A final experimental paradigm would be to use, in culture, postreplicative terminally differentiated cells to investigate agents for their potential to accelerate age-related alterations observed in vivo. Such cell types might be derived through in vitro terminal differentiation, for example, or normal or transformed embryonic neuroblasts or myoblasts. A major concern, however, would be the extent to which the experimental milieu reflected in vivo conditions.

Nonmammalian Animal [Models

Numerous invertebrate species fulfill many of the criteria outlined earlier and have been widely used as models for the study of aging. Some have also been used in studies of genotoxicity. More important, several have already been used to examine toxic effects on aging or age-related processes.

The most widely used and perhaps the only commonly accepted biomarker of aging is life span (Comfort, 1979). Life span has also been the end point most often assayed in invertebrates, although other end points, such as accumulation of lipofuscin and the end of reproductive ability, have also been used. Because of their short life spans, relative ease of use, and relatively low cost, invertebrate organisms will likely be important in the initial phases of a test system to detect environmental toxins that might affect aging or age-related diseases.

Life-table data are a sine qua non of aging research and are therefore essential in a test system to assess toxic effects on aging or age-related diseases. Because invertebrates are often relatively short-lived, it is easy to collect reliable data on the invertebrate of choice. Because such data might not be representative of other genotypes or environments, however, it is often best to choose an organism on which adequate life-table data have already been collected by many investigators over an extended period and under a variety of experimental conditions.

Invertebrates for which adequate life tables are available include fungi, especially *N. craasa* and *Podospora anserina* (Esser and Bockelman, 1985; Munkres, 1985); protozoa, such as *Paramecium tetraurelia* and *Tetrahymena pyriformis* (Smith-Sonneborn, 1985a,b,c); rotifers (Barrows and Kokkonen, 1985); the nematodes *C. elegans, Turbatrix aceti,* and *C. briggsae* (Johnson, 1984; Johnson and Simpson, 1985; Russell and Jacobson, 1985); and insects (Lints, 1985a), especially *D. melanogaster* (Baker et al., 1985; Lints, 1985b), but also *Musca domestica* (Chesky, 1985; Sohal and McArthur, 1985), *Habrobracon juglandis,* and *Tribolium confusum* (Soliman, 1985). Several other invertebrate animal species, less widely studied (Lints, 1985c; Mitchell and Johnson, 1984), and plants (Nooden and Thompson, 1985), whose mode of senescent action has been widely explicated, have also been used as models for the study of aging.

Of the organisms that have been widely used in aging research,

four are of particular interest because they fulfill many of the criteria outlined earlier: *P. tetraurelia,* which has a replicative life span of about 200 cell divisions, encompassing about 40 days (Smith-Sonneborn, 1985b,c); *C. elegans,* which has a mean life span of 10–30 days, depending on temperature and food (Johnson and Simpson, 1985); *D. melanogaster,* which survives an average of about 40 days (Baker et al., 1985); and *M. domestica,* which has a life span of only about 2 weeks (Chesky, 1985). Only two (the nematode C. *elegans* and the fruit fly *D. melanogaster*) are widely used in other kinds of biologic research and are amenable to the wide range of molecular and genetic analyses currently available in the biotechnologic armory.

Some protozoa have little ability to continue mitotic replication in the absence of mating and so have been used to study the phenomenon of finite proliferative life span, usually termed clonal aging (Smith-Sonneborn, 1984). Protozoa display a spectrum of finite replicative divisions among different species, ranging from about 40 divisions to apparent clonal immortality. Probably the best-studied species in aging research is *Paramecium aurelia,* whose age-related morphologic changes have been described during clonal aging, including micronuclear, macronuclear, and cytoplasmic changes. Functional changes in the rate of macromolecular syntheses have been reported. *Paramecium* has been used in assessing the effects of environmental insults, particularly radiation, on clonal life span and replication rate (Smith-Sonneborn, 1985c). Classical genetics is available for many protozoa, including *Paramecium.* Molecular genetic analysis is well developed in some species, but is almost completely lacking in *Paramecium,* and studies are limited to a few laboratories.

Nematodes, particularly *C. elegans* and *T. aceti,* have been widely studied as models of metazoan aging (Johnson, 1984; Johnson and Simpson, 1985; Russell and Jacobson, 1985). The somatic cells of adult nematodes are all postreplicative; mean life spans are a few weeks; and kinetics of death display the Gompertzian increase in mortality seen in higher metazoans. A variety of morphologic, behavioral, physiologic, and molecular changes occur over the life span of the nematode (Johnson and Simpson, 1985); some mimic changes observed in the mammalian aging processes, such as loss of general motor ability (Bolanowski et al., 1981; Johnson, 1987) and lipofuscin accumulation (Clokey and Jacobson, 1986). The animals can be grown on a simple bacterial diet

or in a completely defined medium (Johnson, 1984; Russell and Jacobson, 1985).

C. elegans is the object of study in about 50 laboratories throughout the world. Sophisticated classical and molecular genetic analyses on this organism are available (Russell and Jacobson, 1985), including genetic transformation (Fire, 1986). The entire cell lineage, from one-cell stage to adult, has been described (Sulston et al., 1983). Mutagenesis by transposable elements and DNA transformation are available. A range of genetic variants with lengthened life span are also available (Friedman and Johnson, in press; Johnson, 1987).

Nematodes have been widely used as models in genetic toxicology, as well as in the ascertainment of the effects of drug treatments on life span (Johnson, 1984; Johnson and Foltz, 1987). It would be inappropriate to expect to model all aging processes of humans in any invertebrate. For example, all somatic cells in *C. elegans* adults are postreplicative and therefore do not mimic replicating mammalian cells.

D. melanogaster, the most widely studied invertebrate species, has been the most widely used in aging research (Baker et al., 1985). *Drosophila* has life spans of a few months and can be maintained in the laboratory conveniently under well-defined growth conditions. A wide variety of morphologic, behavioral, physiologic, and molecular changes with age have been described (Baker et al., 1985), some of which parallel changes observed in mammals.

Most important, the fruit fly has been intensively studied for over 70 years as a genetic model and for over 60 years as a general genetic model of metazoan aging (Lints, 1978). Studies have been completed with a wide variety of dietary supplements, environmental insults, and potential toxins to assess the effect of these substances on life span (Baker et al., 1985). Sophisticated molecular genetic techniques are available, including almost routine transposable-element mutagenesis and molecular cloning (Spradling and Rubin, 1982). More is known about the genome of this organism than about that of any other higher metazoan, including the human. Moreover, long-lived strains of *Drosophila* have been derived by selective breeding (Luckinbill et al., 1984; Rose, 1984).

Except for *Drosophila,* the house fly *Musca domestica* is the most widely used insect model for aging research (Lints, 1984). *Musca* is easy to maintain, and mean life spans are around 20

days. Molecular assays can be performed on single flies. A variety of morphologic, behavioral, molecular, and physiologic characteristics display changes over the life span (Chesky, 1985). The free-radical theory of aging has been most directly examined in *Musca* with detailed physiologic and molecular assays (Chesky, 1985; Sohal, 1981). Drugs have been used to modify the life span and physiology in an effort to test the free-radical model further. Unfortunately, almost no classical or molecular genetic analysis of the house fly is available (Chesky, 1985).

The fungi *N. crassa* and *P. anserina* have been widely exploited both in aging research and in classical and molecular genetic analyses. The haploid nature of the fungi makes them especially amenable to the identification of some types of mutations, and both of these fungi have been used to characterize the only senescence phenomenon understood at the molecular level (Esser and Bockelman, 1985). Most molecular genetic techniques are also available for use with these fungi.

Many invertebrate species can be grown under rigorously defined culture conditions. *C. elegans* can be cultured on chemically defined media and cells of *D. melanogaster* can be grown in culture. Although many invertebrates have been examined in aging research, *D. melanogaster* and *C. elegans* are widely used not only in aging but also in other fields, and thus should be emphasized.

The lack of adequate pathology is a major limitation in the use of many invertebrates. For example, only sparse pathologic descriptions at death are available for *Drosophila* at the electron microscopic level (Baker et al., 1985) and for *M. domestica* (Chesky, 1985; Sohal and McArthur, 1985). Only a minimal description, at the electron microscopic level, of senescent changes in *C. elegans* has been made (Johnson, 1984).

Invertebrates are phylogenetically far removed from mammals and might therefore differ from them in fundamental ways. Although many studies of basic biochemical and physiologic events have shown that these processes are conserved over large phylogenetic distances, it is clear that not all physiologic processes are conserved. The lack of information on the nature of basic aging processes in any metazoan makes it impossible to determine, a priori, the relevance of any organismic model to human aging. Nevertheless, in some important applications, such as assessment of toxic effects on life span and modification of life span by toxic

agents, invertebrates are useful models and are cost-effective alternatives to mammalian models.

Mammalian Models

Most mammals do not fully meet the criteria of a short life span, relative ease of maintenance in a defined environment, wide use in biologic research, and suitability for a wide variety of molecular and genetic analyses. Mice and rats best fulfill these and other criteria for aging research (National Research Council, 1981b), and indeed they have been and are widely used in aging research.

Many vertebrate species, such as rabbits (National Research Council, 1981b), lack good life-table data, although they are often used as models for atherogenesis research. It is difficult to obtain a rabbit more than 5 years old, not because of spontaneous death, but because breeders usually kill the animals by that age. Two studies have addressed the longevity characteristics of rabbits; one indicated a life span of 8 years (Weisbroth, 1974) and the other of 13 years (Flower, 1931). Before rabbits can be effectively used in aging research, further information concerning their longevity is necessary.

Even when excellent life-table data are available, investigators often fail to make use of them in designing their aging studies. Prominent biochemists and metabolic physiologists commonly draw conclusions about age-related changes in a biochemical process on the basis of a study limited to 2-month-old and 6-month-old rats in a strain with a life span of 48 months. Although such studies are of value, a broader range of ages should be studied if the influence of age on biochemical activity is to be adequately defined.

The value of published pathologic data is illustrated by the following example. The male Fischer 344 rat is a popular model for aging studies. More than 50% of these rats have testicular interstitial cell tumors at the age of 18 months, and by the age of 24 months almost all have the tumors (Coleman et al., 1977; Yu et al., 1982). That information is critically important in designing studies on the aging of the male reproductive system. It is also important to carry out pathologic analyses in the same animals on which physiologic or biochemical measurements are being made. For instance, if the concentration of serum parathyroid hormone increases in some but not all old male Fischer 344 rats, it is important to know whether this increase could be secondary to a

coexisting disease process, for example, a severe grade of chronic nephropathy.

Rats have the advantage of providing more biologic material per animal than mice without markedly increasing the maintenance cost or space requirement. A disadvantage is the small number of inbred strains available (National Research Council, 1981b). The Fischer 344 strain is the major inbred rat strain that has been used in aging research. It has several advantages in addition to genetic homogeneity: it does not become obese with advancing age (Bertrand et al., 1980a), extensive data on its age-related disease processes have been published (Coleman et al., 1977; Maeda et al., 1985), and there is a sizable body of life-table data (Masoro, 1980; Yu et al., 1982, 1985).

The major disadvantage is the occurrence of progressive chronic nephropathy and renal failure in animals fed ad libitum at a relatively early age (Maeda et al., 1985). Restricting the rat strain to 60% of the ad libitum food intake prevents the progressive chronic nephropathy. The National Institute on Aging is developing Brown-Norway, Fischer 344 F_1 hybrids for the purpose of partially circumventing chronic nephropathy. It is already clear that a controlled and defined dietary progam is necessary in aging studies.

Other rats that have been extensively used for aging research are the Sprague-Dawley, Wistar, and Long-Evans (Masoro, 1980). They are not inbred strains and are not genetically homogeneous. It is more appropriate to call them stocks than strains (National Research Council, 1981b). Life-table data are available (Masoro, 1980). A comprehensive report (Anver et al., 1982) on the age-related disease processes of the male Sprague-Dawley rat is available. A disadvantage of the male Sprague-Dawley and Wistar rats, compared with male Fischer 344 rats, is that they become obese with advancing age (National Research Council, 1981b).

Because they are small, mice are relatively inexpensive to maintain and do not require a large space. Moreover, many inbred strains are available, and some are even available as aged animals (see Appendix A), which facilitates genetic exploration of aging (National Research Council, 1981b). A disadvantage of mice is that only a small amount of biologic material can be obtained from a single animal. Good life-table data are available on several strains (National Research Council, 1981b): C57BL/6N Nia males, BALB/cN Nia males, CB6F males, C57BL/6J females,

DBA2/J females, B6D2F females, C57BL/6J males, DBA2/J males, $B6D2F_1$ males, C3Hf/Bd females, BALB/c An Bdf females, C3CF females, C3Hf/Bd males, BALB/c An Bdf males, and $C3CF_1$ males.

Inbred strains often suffer from a single major disease process (e.g., cancer of the liver or chronic nephropathy), and the presence of this major disease process in most if not all the animals complicates gerontologic interpretation. F1 hybrid strains offer a partial solution to the problem and can be readily produced in large numbers. McClearn et al. (1970) have developed a more genetically heterogeneous stock of mice that is systematically maintained. Their procedure yields a genetically stable population without the drawback of inbred strains and thus probably provides a model for aging research in which genetic variation is readily accessible. Recombinant inbred strains (Bailey, 1981) should also be more widely used. Because of the genetic identity of each member of a population, some individuals can be sacrificed while identical siblings are maintained for survival and analyses on living animals (Johnson, 1987).

If old animals are available from suppliers, the investigator must also make certain of the availability of accurate information on the lifetime environment of the animals, including dietary history and data on the monitoring of infectious disease. Usually, such data are not available on long-lived animal models of advanced age. Indeed, the lack of well-defined animals and the cost of their purchase and maintenance have made it difficult to carry out aging research on adequately characterized long-lived animal models. Reasonable life-table data are available on the beagle and the thoroughbred horse.

With regard to nonhuman primates, the two principal models that appear to be emerging are the pig-tailed macaque monkey *(Macaca nemestrina)* (Bowden, 1979) and the rhesus monkey *(Macaco, mulatta)* (Davis and Leathers, 1985). It might be desirable to develop aging cohorts of the chimpanzee because, from a biochemical and genetic point of view, chimpanzees are closely related to man; but practical considerations limit the feasibility of this model.

The availability of tissues and fluids from a selection of mammalian species of contrasting life spans, ranging from the short-lived murine species to the long-lived primates, would permit a

systematic comparative approach to the study of aging. For example, it would permit the differentiation of markers that appear to be related primarily to chronologic rather than biologic age, and thus provide a stronger rationale for the choice of assays for the effects of agents that might alter aging processes.

Epidemiologic Models

The expression "experiments of nature" refers to contrasts in the exposure of human populations to toxic agents that provide an opportunity to assess the impact of toxic exposures on the risk of disease and death in the human population. Many reports of acute and chronic releases of toxic agents into the human environment gave rise to marked contrasts in toxic exposures and disease outcomes. They include the mercury contamination of Minimata Bay in Japan, the atomic blasts in Hiroshima and Nagasaki, and smog episodes in London.

The first of the well-publicized air-pollution incidents that resulted in marked increases in illness and death, mostly among the elderly, occurred in the Meuse River Valley in Belgium in 1930. This heavily industrialized area was seriously affected when accumulating air contaminants, trapped by an inversion resulting from a thick, cold fog, caused 60 deaths and illness in thousands of residents. The incident at Donora, Pennsylvania, in 1948 resulted from a similar inversion that covered a wide area of the northeastern United States, including the industrial community of Donora. Of the population of 14,000, 20 died (compared with the expected 2 deaths for the period) and 43% fell ill. Again, the elderly were the most seriously affected. Similar episodes of smog-induced mortality in London as early as 1873 and in New York City during the 1950s and 1960s have been described (Amdur, 1986).

In all those episodes, the most vulnerable people were the elderly and those with pre-existing disease of the cardiopulmonary system. Organic mercury compounds, specifically methyl and ethyl mercury salts, are of toxicologic importance because they pass through the blood-brain barrier, accumulate in the brain, and can produce irreversible damage to the central nervous system. Chronic exposure to these compounds might occur in the workplace or in the general environment.

Intense interest in the toxicity of methyl mercury developed in the 1950s, when a neurologic illness, now called Minimata disease,

appeared in the families of fishermen living around Minimata Bay in Japan. The bay water was contaminated by mercury waste (inorganic and methyl mercury) from a local chemical plant. Investigation determined that the illness resulted from the repeated ingestion of large quantities of fish in which the mercury concentration was thousands of times that in the water (Goyer, 1986).

The cancer experience of the Japanese atomic-bomb survivors in Hiroshima and Nagasaki has been carefully assessed in relation to the estimated whole-body doses received by individual survivors. The Life Span Study sample of the Radiation Effects Research Foundation includes 82,000 atomic-bomb survivors and 27,000 nonexposed comparison persons, among whom 19,606 deaths had occurred by 1974 (Beebe, 1979; Beebe et al., 1978).

These studies have been extremely informative about radiation-related solid tumors as well as leukemia. For example, they documented the striking difference in the minimal latent periods, with the minimal period for solid tumors being about 10 years, compared with 2 years for leukemia. Age at time of exposure appears to be a strong determinant of leukemia risk; the greatest absolute risk is experienced by those exposed at ages 0–9 and 50 years and over.

Leukemia was the first cancer reported in excess among atomic-bomb survivors, but in the most recent followup studies, the later-appearing solid tumors appear to be as important as leukemia in terms of absolute risk. Most of the excess cancer deaths from solid tumors among the atomic-bomb survivors have occurred in those over 35 at the time of the blast. It appears, therefore, that the radiation effect manifested as lung, breast, and other solid tumors is observed only in people who have reached the age range normally associated with the incidence of cancer.

LIFE-SPAN MODULATION BY DRUG TREATMENT

The effects of toxic agents on aging or aging processes have not been widely studied (Schneider and Reed, 1985). Some of the best studies carried out so far have concentrated on the effects of drugs that alter oxidative stress. Usually, mean life span and often maximal life span are used as the end points in assessing the effectiveness of experimental interventions in such studies, although in a few cases lipofuscin accumulation and other end points have been used (Balin, 1982).

Although several examples of extension of mean life span in mice, in nematodes (Balin, 1982), in *Drosophila* (Baker et al., 1985), and in house flies (Sohal and Allen, 1986) have been reported, the studies have not been highly replicated and have sometimes been complicated by design flaws. For instance, treatment often affects only mean and not maximal life span, or treatment might reduce early life trauma and death, but have no effect on aging itself. Studies might also be complicated by effects of the drug treatment on food intake, in that food intake or body weight is significantly decreased by the drug (Balin, 1982). No single drug treatment or dietary additive has been reliably shown to extend life span in any organism.

8

Conclusions

The elderly constitute the fastest-growing segment of the population in many industrial countries. This unprecedented demographic phenomenon is occurring at a time of increasing complexity of environmental factors, including pollutants, pharmaceutical use, nutrition, and life-style. The impact of these environmental phenomena on aging processes and the aged is not well understood, but there are sound biologic reasons to assume that the effect of the environment on people changes with age, as does the ability to respond to environmental exposures.

In addressing the issues related to aging in today's environment, one must recognize at least three important questions: What is the nature of aging? What is the nature of the environmental exposure? What is the physiologic or medical condition of the aging or aged subject or population?

The nature of the aging processes has been a question since humans have been aware enough of themselves to ask it. Not much progress has been made toward answering it.

Environmental exposures vary greatly among individuals. Such exposures might well be more problematic for the aged, especially those with existing chronic diseases. Over 70% of the aged take one pharmaceutical regularly; and heart disease occurs in over 25%. These changes in physiologic and medical conditions

of aging reflect the effects of the environment on intrinsic aging processes integrated over a person's lifetime.

In addition, it should be understood that the term aged means different things to different people. More important, aged simply refers to a portion of the normal distribution of ages in any population defined by any number of objective, functional, or other criteria.

After extensive review of the current state of the science and after deliberation of the above questions, the committee drew the following conclusions.

Evidence supports the concept of intrinsic aging, and many theories have provided insight into its basic mechanisms. Numerous components of the environment have been shown to cause changes that simulate and are often confused with features of intrinsic aging. For example, habitual sun exposure and cigarette smoking accelerate aging of the skin, exposure to ultraviolet radiation promotes cataract formation, and exposure to naturally occurring or industrial or other toxicants can contribute to age-related neurologic disease. However, no single agent has ever been shown to cause the earlier appearance of *all* aging processes.

Humans exhibit varied responses to the environment and varied patterns of aging. The variation can be attributed to many factors, which include the following:

- Differences in individual environment, including nutrition, pharmaceuticals, life-style, and occupation.
- Inborn genetic differences, such as variations in genes that influence susceptibility to graying of the hair, cataract formation, diabetes, aging of sun-exposed skin, and metabolism of drugs.
- Interactions between individual genetic constitutions and the environment.

Information on the specific impact of environmental factors on aging processes remains scant. However, experimental animal studies of dietary restriction and genetic manipulations (e.g., selective breeding) that extend the life spans of some laboratory animals are promising tools for the study of aging processes and the impact of the environment on them.

With regard to the human aged, not enough is known about the specific effects of environmental exposures, but there is much evidence of their importance. Consider the following, for example:

- Extremes of air pollution or environmental temperature that are tolerated by young adults can be injurious, even fatal, to the elderly.
- Although the judicious use of medications undoubtedly contributes to the overall well-being of older persons, they suffer adverse reactions to drugs more frequently than the young. The extent to which that is due to disease severity, use of multiple drugs, drug misuse, or age itself is unknown.
- Older persons are often more susceptible than young adults to the effects of environmental toxicants.
- A decrease in smoking, an increase in exercise, control of hypertension, and dietary modification appear to decrease or delay the occurrence of heart disease, stroke, and some types of malignancy.
- Interpersonal relationships can have substantial positive effects on various physical health indexes, and sense of purpose is closely tied to the health and well-being of the elderly. There is evidence of greater survivorship among people who have goals than people who do not, and among those who have organization in their daily lives and behavior than those who do not. Health-care providers, in nursing homes in particular, should be educated about the benefits to the elderly of increased autonomy and friendships.

Although the increased incidence of chronic diseases is often associated with aging, such diseases need not be characteristic of the aging processes. The wide variation in the incidences of chronic diseases in the aged in different countries strongly indicates that much of the prevalence of these diseases might be preventable. One appealing and testable hypothesis is that reduction of disease in old age is an attainable objective that can be approached, in part, through modification of the environment. Research in this field will likely lead to an improved understanding of the interplay between aging processes, the environment, and disease and help to provide the key to preventing environmentally induced age-associated diseases.

9

Recommendations

In view of the paucity of basic information on aging processes, it is premature to embark on a systematic screening of environmental agents with an eye to identifying agents that influence these processes. Such an approach would be ill-advised and detrimental to progress in the field of "gerontotoxicology," the study of interactions between aging processes and the effects of environmental substances with toxic potential. Rather, there is a need to develop a better understanding of the basic mechanisms of aging, how they can be affected by the environment, and how aging itself affects toxicity. The following is a list of recommendations related to research, education, and resources; the order in which they appear does not imply priority.

RESEARCH

- The identification and elucidation of the fundamental mechanisms of aging are essential. The effects of environmental agents on aging processes, in the causation of age-related diseases, and in the susceptibility of the aging population cannot be fully understood without such knowledge. In this regard, the search for valid biomarkers of aging to assess the impact of environmental factors on aging processes and the aged should be continued.

- The effects of dietary restriction and nutritional constituents on life span and specific physiologic functions should be studied by both gerontologists and toxicologists, especially because these factors might influence the effects of toxic environmental agents.
- Toxicity data on older organisms should be collected as part of the normal toxicity testing of agents. These data should include toxicokinetics and pharmacodynamics.
- The responses of aged laboratory animals to specific toxic agents should be studied as useful descriptors of the aged state.
- To conserve resources, the testing of aged animals should generally be restricted to the study of specific experimental issues rather than aimed at screening environmental agents.
- Although general screening is inadvisable, toxicologists should identify a group of archetypal toxic agents (reference compounds) and nontoxic agents (negative controls) that could be used to mimic age-associated diseases or biologic markers of aging. Such agents (e.g., methylphenyltetrahydropyridine, MPTP, which selectively kills cells in the substantia nigra and causes a parkinsonian syndrome) provide unusual opportunities for basic research on mechanisms of aging and the environmental impact thereon. Current theories of aging should be used to guide the selection of agents that hasten or retard hypothetical aging processes.
- With regard to nervous system disorders, prevention can be regarded as a realistic goal, if the cause of subclinical damage can be identified. Epidemiologic attention should be focused on early environmental exposures that can predispose to neurologic disorders later in life. Causal mechanisms that underlie both environmental damage and the changes associated with aging should be sought.
- The roles of genomic instability and chemical free radicals should be studied in view of the current understanding of mechanisms of aging and evidence of their involvement in the promotion of age-associated diseases.

- Populations on which information about toxic exposure is available should be the subject of epidemiologic studies of age-associated characteristics and diseases. Persons exposed to specific chemical substances in an industrial setting or as a result of an "experiment in nature" should be followed throughout life, so that the effects of such exposure that have long latent periods can be identified and investigated. Special attention should be given to populations in which age-associated conditions and diseases of presumed environmental origin are present in unusually high incidences (e.g., the high incidence of parkinsonism and Alzheimer-type dementia in Guam and elsewhere).
- Genetic susceptibility to the effects of drugs and their biotransformation, as well as multiple drug therapy and severity of disease, might account for the apparent increase in the incidence of adverse drug reactions with age. Efforts to evaluate the effects of age itself on the disposition (absorption, distribution, metabolism, and elimination) of drugs and other chemicals should continue.
- The elderly often take multiple drugs and vitamins and are exposed to other environmental agents, and the potential detriments to health need to be evaluated. Information on age and nutritional and disease status of the elderly and on type, dosage, and duration of exposure can usually be established with some accuracy and with only modest cost.
- Research is needed on the effects of advanced age on pharmacokinetics, bioaccumulation, and other drug and chemical interactions—including the effects of inducers and inhibitors of hepatic drug-metabolizing enzymes—and the influence of dietary factors, smoking, and other environmental factors.
- Research on variations among the aged in susceptibility to the effects of pharmacologic agents and related environmental chemicals should consider the impact of polymorphisms at relevant genetic loci. The frequencies of such polymorphisms might be different among the elderly surviving members of population cohorts.
- The short- and long-term effects of drugs and chemical substances should be investigated as functions of age in an attempt

to assess the potential unique susceptibilities of the elderly human population.

- Efforts to develop animal model systems of aging (whole animals, organs, tissues, and cells) should be increased.
- Efforts to establish systematic autopsy studies are encouraged. They should include both randomized age-representative samples of deaths and samples of deaths of people who were exposed to high concentrations of environmental agents and were followed prospectively.

EDUCATION

- The general public and health-care providers should be better informed about nutritional needs of the healthy elderly and of those who suffer from age-associated diseases and about lifelong nutritional programs aimed at preventing or delaying the onset of age-associated diseases and related problems.
- Various modes of education, including the mass media, should be used to warn the lay public and health-care providers against unsubstantiated dietary regimens purported to extend life and prevent disease. It should be understood that there is very little evidence that such diets influence the human aging processes. Moreover, there is no evidence that their long-term use will not adversely affect the health of humans.
- The evidence that links specific environmental factors to specific disorders in the elderly should be more widely disseminated in simple language, for example, the adverse effects of smoking, of exposure to ultraviolet radiation, and of inappropriate nutrition.
- The scientific community should be encouraged to focus attention, through its professional societies, on gerontotoxicology. This combination of the fields of toxicology and gerontology should be given prominence in seminars, symposia, and other programs at annual meetings and special meetings. Topics that deserve attention include: models and methods for studying chronic toxicity

and mechanisms of aging; comparative toxicology in young and old mammals; neurotoxicology and aging; immunotoxicology and aging; genetic toxicology and aging; toxicokinetics, toxicodynamics, and aging; and the role of diet, including toxic factors in some foods, in aging.

- Both government and private initiatives in the training of professionals and the development of academic programs that require skills at the interface of gerontology and toxicology should be encouraged. Suggested goals include: development of training grants for predoctoral and postdoctoral students, summer institutes and sabbaticals for established investigators, and improved nutrition education in medical schools.

FUNDING AND RESOURCES

- The committee urges those who carry the heavy responsibility of setting priorities for the use of what are always finite resources to consider the potential advantages of advances in the knowledge of aging and the environment. There is substantial potential to improve the quality of life during a period that every person hopes to face and the possibility of elucidating other processes, such as cancer and heart disease, through the study of aging.
- The use of animals as models for the study of aging and toxicity has made important contributions to knowledge in these fields. Efforts to develop aged animals generally should be encouraged, so that adequate numbers are available for gerontotoxicologic research.
- Additional efforts are needed to develop banked collections of cells, tissues, and fluids for future research. The existence of a system to ensure the collection, storage, and study of relevant tissues, cells, and body fluids would support studies of body burdens of environmental agents and the consideration of potential causal associations of these agents with tissue changes over time.
- The likely impact of the demographic shift that is now under way and will continue into the twenty-first century will be to

alter fundamentally the major social and economic commitments of this country. The development of interventions that enable the elderly to live out their lives independently and productively will mitigate the impact. Support of research into aging and into the effects of the environment on aging processes should therefore be given a high priority.

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Appendix

Resources for Studying Aging

INVERTEBRATES

Caenorhabditis Genetics Center (CGC), Division of Biological Sciences. University of Missouri, Columbia—CGC acquires, stores, and distributes genetic stocks of *Caenorhabditis elegans* (a nematode) and relevant bibliographic and genetic information. It receives nematode strains and mutants and reprints of related publications and data (raw and analyzed) relevant to nematode genetics; stores these materials; verifies genetic status or scientific accuracy; distributes bibliographic and genetic information on mutant strains to individual scientists and, through publications, to the scientific public at large; and distributes mutant strains to interested scientists. CGC has multi-institute support and the advantage of multidisciplinary input into its data bases, which permits it to support a wide range of research interests.

CELL CULTURES

Aging Cell Culture Repository (ACCR), Cornell Institute for Medical Research, Camden, New Jersey—ACCR acquires, develops, characterizes, stores, ands supplies cell cultures for gerontologic research. It contains over 600 cell cultures available for research

on aging, including over 200 skin fibroblast cultures from healthy persons of various ages who are participating in the Baltimore Longitudinal Study on Aging at the Gerontology Research Center; skin fibroblast cultures from persons with premature-aging syndromes, including Hutchinson-Gilford syndrome (progeria); and cultures from clinically documented and at-risk persons, as well as entire families exhibiting familial Alzheimer's disease. Also available are human and WI-38 female diploid lung cells available at early, middle, and late population doubling levels. Cultures of animal origin include skin fibroblasts from a variety of species of nonhuman primates, bovine and equine endothelial cells, smooth muscle and fibroblast cultures, and canine and porcine endothelial cells.

EXPERIMENTAL POPULATIONS

Biomarker Research Program, National Institute on Aging (NIA) and National Center for Toxicological Research (NCTR)—NIA, in conjunction with NCTR, is in the process of developing a colony of rodents to be used specifically for a biomarker research program. Those being developed for NIA will be used to develop biomarkers of aging. Those being raised for NCTR will be used to develop biomarkers of toxicity, to evaluate the critical assumptions used in risk assessment. This is a unique program, in that two major institutions of the Public Health Service have joined forces in the use of uniform strains, species, and laboratory conditions to elucidate similar end points for different purposes related to their independent missions. The core of this colony will include four mouse genotypes (C57BL/6NNia2, DBA/2NNia2, B6D2F1Nia2, and C3B6F1) and three rat genotypes (F344Nia, BN/BiRijNia, and the F344BNF1 hybrid), which will be maintained similarly to the other colonies, but fed either ad libitum or under conditions of restricted feeding. These colonies will be unique, in that ultimately it will be possible to compare the rodent strains used for gerontologic studies with those used for toxicity testing under a range of conditions. Research availability of the animals will be limited for gerontologic investigations to those selected by NIA (through grant or contract mechanisms) and for toxicologic investigations to those selected by NCTR for biomarker research.

RODENTS

Inbred Strains

National Institute on Aging (NIA)—Specific-pathogen-free rodents available or under development from NIA include three rat and 10 mouse genotypes that are raised in barrier facilities and range in age from 3 to 36 months. Available mouse genotypes are inbred strains A/HeNNia, BALB/cNNia, CBA/CaHNNia, C57BL/ 6NNia, and DBA/2NNia; hybrids of B6C3F1Nia (C57BL/6NNia X C3H/NNia), B6D2F1Nia (C57BL/66NNia X DBA/2NNia), and CB6F1Nia (BALB/cNNia X C57BL/6NNia); the congenic strain BALB/cAnNNia-nu(nude); and outbred stock of Swiss Webster. NIA provides a rat genotype, the inbred Fischer 344 (F344NNia); however, a colony of three additional genotypes is under development: the inbred Brown Norway (BN/BiRijNia) and the reciprocal F1Nia hybrids of the F344 and BN crosses. All rodents are regularly monitored for genetic purity and health status.

Outbred Strains

National Center for Toxicological Research (NCTR)—Specificpathogen-free (SPF) rodent resources currently available or under development include *Mus musculus* (house mouse) and *Peromyscus leucopus* (white-footed mouse). Specimens of both species were obtained from colonies that were started with founder stocks trapped in woodlots and old fields at Argonne National Laboratory in 1962–1964 and bred in the Argonne animal facility by random out-crossing. The colonies have been enlarged and random out-crossing maintained since their transfer to NCTR in 1982. Specimens of *M. musculus* range in age from weanling to 37 months. Specimens of *P. leucopus* range in age from weanling to 84 months. Both species were housed in SPF facilities and fed laboratory diet NIH-31 and water ad libitum. The animal rooms are maintained at 70°F±2°F and 40%±3% relative humidity under artificial illumination with a 12:12 light:dark cycle. Cages are routinely rotated on cage racks to prevent retinal degeneration from fluorescent lighting. These colonies are small, so animals are not routinely shipped to other laboratories; however, access to them for study is available. No charge is made for onsite use.

NONHUMAN PRIMATES

National Institute on Aging (NIA)—NIA maintains approximately 300 nonhuman primates (mainly *Macaco, mulatta,* with a few *M. nemestrina*) at five regional primate centers for conducting research on aging. The animals are approximately 18–35 years old. About two-thirds are available for noninvasive research, and the remaining one-third for invasive research.

Committee Biographies

ROBERT N.BUTLER (co-chairman) is Brookdale Professor and chairman of the Gerald and May Ellen Ritter Department of Geriatrics and Adult Development, Mount Sinai Medical Center, New York City—the nation's first medical-school department of geriatrics. He was a principal investigator in one of the first comprehensive longitudinal studies of the health of community-residing elderly, conducted by the National Institute of Mental Health (1955–1966). He was founding director of the National Institute on Aging (1975–1982). In 1976, he won the Pulitzer Prize in nonfiction for *Why Survive? Being Old in America*. Dr. Butler is editor-in-chief of *Geriatrics*. He is a member of the Advisory Council of the New York-New Jersey Center on Environmental and Occupational Health, chairs programs for the Commonwealth Foundation and Brookdale Foundation, serves on the U.S. Congress Physicians Payment Review Commission, and helped found the American Federation for Aging Research and the Alzheimer's Disease and Related Disorders Association, on whose boards he serves.

EMIL PFITZER (co-chairman) is assistant vice-president and group director of the Department of Toxicology and Pathology at Hoffmann-La Roche Inc., where he is responsible for the design, conduct, and interpretation of toxicologic chemicals. He holds

appointments as adjunct professor at Rutgers University and the New York University Institute of Environmental Medicine. He was president of the Society of Toxicology in 1985–1986 and is a member of a number of national scientific organizations. He was certified in general toxicology by the American Board of Toxicology, Inc., in 1980. In addition to his work at Hoffmann-La Roche Inc., he has served on the National Institute of Environmental Health Sciences Training Grant Review Committee, on advisory boards for the National Center for Toxicological Research and the Brookhaven National Laboratory Medical Department, and on several National Research Council committees. Dr. Pfitzer's publications include several book chapters on the principles of dose-effect and dose-response relationships.

PATRICIA A.BUFFLER is professor of epidemiology and director of the Epidemiology Research Unit in the University of Texas Health Science Center, Houston School of Public Health. She has served on numerous National Research Council committees, as chairman of the World Health Organization Expert Committee on Women, Work, and Health, and on various other expert and research review groups for the National Institute for Occupational Safety and Health, National Institutes of Health, U.S. Environmental Protection Agency, U.S. Department of Energy, and WHO. Dr. Buffler is the immediate past president of the Society for Epidemiologic Research and is a member of the executive board of the American College of Epidemiology. Her current research is in the epidemiology of occupational cancer, reproductive risks, pulmonary diseases, and epidemiologic studies of environmentally induced disease.

FREDERICK J.DE SERRES is director of the Center for Life Sciences and Toxicology in the Research Triangle Institute in North Carolina. His numerous publications include papers on the genetic effects of radiation and environmental chemicals and on the development, validation, and use of short-term tests to detect environmental mutagens and carcinogens. He has served as chairman of the WHO/International Program on Chemical Safety's working group on the validation of short-term tests for carcinogens. He serves as chairman of several national and international committees dealing with toxicology. He is a member of the American Environmental Mutagen Society, the European Environmental Mutagen Society, the American Association for Cancer Research,

the Genetics Society of America, and the International Commission for Protection Against Environmental Mutagens and Carcinogens. He also serves as adjunct professor of pathology at the University of North Carolina, Chapel Hill.

BARBARA GILCHREST is professor and chairman of dermatology at Boston University School of Medicine and senior scientist at the USDA Human Nutrition Research Center on Aging at Tufts University. She is chairman of the Aging Review Committee of the National Institute on Aging, a member of the National Scientific Advisory Council of the American Federation for Aging Research, director of the American Board of Dermatology, and a member of the board of directors of the Society for Investigative Dermatology. Her research involves the effect of chronologic aging and environmental impact on the behavior of cultured skin-derived cells. Dr. Gilchrest is the author of more than 130 articles, reviews, textbook chapters, and abstracts and the author/editor of two recent books concerning skin aging.

RONALD W.HART is director of the National Center for Toxicological Research, a position he has held since 1980. Before joining FDA, he served as professor of radiology with cross appointments as professor in medicine and zoology and the Ohio State University, Columbus, Ohio. Currently, he holds adjunct professorships at the University of Arkansa for Medical Sciences at Little Rock, Arkansas and the University of Tennessee Center for the Health Sciences at Memphis, Tennessee. He has published numerous articles on toxicology, gerontology, carcinogenesis, biochemistry, molecular biology, organic chemistry, and radiation biology/oncology.

Dr. Hart serves as chair of the Department of Health and Human Services' Committee to Coordinate Environmental Health and Related Programs; chair of the Science Panel's Cabinet Council Agent Orange Working Group; and chair of the Color Additive Scientific Review Panel. He has served as a member of the National Research Council's Board on Toxicology and Environmental Health Hazards, and as chairman of the White House Office of Science and Technology Policy's Task Force on Chemical Carcinogens for a review of the science and its associated principles of the consensus workshop on formaldehyde, of the international consensus symposium on risk assessment, and of the World Congress on Toxicology. He has received the Karl-August-Forster Award, the

FDA Award of Merit, the Public Health Service Superior Service Award, and the Governor's Award for Outstanding Service to the State of Arkansas.

THOMAS E.JOHNSON is assistant professor of molecular genetics in the Department of Molecular Biology and Biochemistry in the University of California, Irvine. Dr. Johnson is a fellow of the Gerontological Society of America and the American Federation for Aging Research and is active in both those organizations. He is a member of the Genetics Society of America, the Society for Developmental Biology, and the Behavioral Genetics Association. He has served as a reviewer for most major journals in biologic gerontology and genetics and for the National Institutes of Health, the National Science Foundation, and the U.S. Department of Agriculture. His research interests are in the genetic dissection of the aging processes, primarily through the use of long-lived genetic variants of the free-living nematode *Caenorhabditis elegans*.

CARL KUPFER is director of the National Eye Institute, in which capacity, he is responsible for laboratory and clinical research programs in vision in the intramural laboratories and in research organizations nationwide. His interests also extend to activities regarding blindness in the developing world. He is president of the International Agency for the Prevention of Blindness, director of the World Health Organization (WHO) Collaborating Center at the National Eye Institute, and a consultant to WHO.

GEORGE MARTIN is professor of pathology, adjunct professor of genetics, and director of the Alzheimer Disease Research Center at the University of Washington. He has chaired the National Institute on Aging's Aging Research Review Committee, has been chairman of a task force to develop a National Research Plan on Aging, and has been a member of the National Advisory Council. In 1981, Dr. Martin received the Brookdale Award of the Gerontological Society of America for his research contributions to basic biologic and clinical aspects of gerontology. His major focus has been on genetic approaches to the study of mechanisms of aging.

EDWARD J.MASORO is professor and chairman of the Department of Physiology in the University of Texas Health Science Center at San Antonio. His research focus is the use of nutritional manipulations as tools for studying basic aging processes. He was

a member and chairman of the Aging Review Committee of the National Institute on Aging. He is now chairman of the Board of Scientific Counselors of the National Institute on Aging, editor for biologic sciences of *Experimental Aging Research,* and on the editorial boards of *Journal of Gerontology, Experimental Gerontology,* and *Proceedings of the Society for Experimental Biology and Medicine*.

DAVID M.PRESCOTT is distinguished professor of molecular, cellular, and developmental biology at the University of Colorado, Boulder. He is a member of the National Academy of Sciences and the American Academy of Arts and Sciences and past president of the American Society for Cell Biology. He received a senior U.S. scientist award for 1979–1980 from the Alexander von Humboldt Foundation of the Federation Republic of Germany. He has served on study sections/panels for the American Cancer Society, the March of Dimes Birth Defects Foundation, the National Science Foundation, and the National Institutes of Health. He was editor of *Methods in Cell Biology* and co-editor of *Advances in Cell Biology* and *Cell Biology: A Comprehensive* Treatise. He is author of *Reproduction of Eukaryotic Cells* and *Cell Biology* and co-author of *Cancer: The Misguided Cell.* He served on the editorial boards of *Experimental Cell Research, Cancer Research,* and *The Journal of Biological Chemistry*. His research interests include cell growth and reproduction, structure of genes and chromosomes, cancer biology, DNA replication and sequences, transcription regulation, RNA synthesis and processing, and nucleotide metabolism.

PETER S.SPENCER is professor of neuroscience, neurology, and pathology and director of the Institute of Neurotoxicology in the Albert Einstein College of Medicine of Yeshiva University. He is a member of the Board on Environmental Studies and Toxicology of the National Research Council and a former member of its Committee on Toxicology, and he is a past president of the specialty section on neurotoxicology of the Society of Toxicology. His research activities focus on molecular and cellular mechanisms of age-associated disorders of the human nervous system and especially on the impact of environmental toxins on the health of developing peoples.

ELLIOT VESELL is Evan Pugh Professor of Pharmacology

and chairman of the Department of Pharmacology at the Pennsylvania State University College of Medicine in Hershey, Pennsylvania. He graduated from Harvard College in 1955 and Harvard Medical School in 1959. He did his residency training at Massachusetts General Hospital and Peter Bent Brigham Hospital. From 1960 to 1962 he was a research associate and assistant physician at Rockefeller University. From 1963–1965 he was a clinical associate at the National Institute of Arthritis and Metabolic Diseases, NIH. From 1965–1968, he served in the National Heart and Lung Institute, NIH, as the head, Section on Pharmacogenetics, Laboratory of Chemical Pharmacology. In 1971 he received from the American Society for Pharmacology and Experimental Therapeutics the award for Experimental Therapeutics. In 1985 he was selected for their Harry Gold Award in clinical pharmacology. Also in 1985, he served for three weeks in the United Kingdom as Frohlich Professor of the Royal Society of Medicine. He has been selected twice as Burroughs Wellcome Visiting Professor of Clinical Pharmacology, twelve times as Pfizer Lecturer, and also gave the Allan Bass Lecture at Vanderbilt University and the Hahnemann Lecture at the University of California, San Francisco.

ROBERT E.VESTAL is associate professor of medicine at the University of Washington, Seattle, and associate chief of staff for research and development in the Veterans' Administration Medical Center in Boise, Idaho, where he also is chief of the Clinical Pharmacology and Gerontology Research Unit. For the last 14 years, Dr. Vestal has conducted clinical research on the effects of aging on drug metabolism, drug response, and drug interactions, including the influence of cigarette smoking; he has also edited a book on drug treatment in the elderly. He serves on the editorial boards of *Clinical Pharmacology and Therapeutics, Clinical Pharmacokinetics,* and the *Journal of the American Geriatrics Society* and on the Veterans' Administration Merit Board for Alcoholism and Drug Dependence (Clinical Pharmacology). He is chairman of the executive committee of the clinical pharmacology division of the American Society for Pharmacology and Experimental Therapeutics, vice-chairman of the ad hoc committee on drugs in the elderly of the American Society for Clinical Pharmacology and Therapeutics, and a fellow of the American College of Physicians, the American College of Clinical Pharmacology, the Gerontological Society of America, and the American Geriatrics Society. In

1980, he was a member of the World Health Organization Technical Group on Use of Medicaments by the Elderly.

MARC E.WEKSLER is the Irving S.Wright Professor of Medicine and director of the Division of Geriatrics and Gerontology in the Cornell University Medical Center in New York City. He is an immunologist and cell biologist by training, and his research has defined the cellular and molecular basis of changes in the immune system, in the blood vessels, and in tumor growth that accompany aging. He is the chairman of the Geriatrics Medical Knowledge program of the American College of Physicians and is a consultant to the World Health Organization and U.S. Veterans' Administration. He is a member of the American Society for Clinical Investigation and the Association of American Physicians.

JERRY R.WILLIAMS is professor of oncology and director of the Radiobiology Laboratory at the Johns Hopkins Oncology Center and is a member of the Environmental Health Sciences Department of the Johns Hopkins School of Hygiene and Public Health. He is a member of the Radiation Research Society, the American Society of Photobiology, the European Society of Photobiology, the Environmental Mutagen Society, the Gerontological Society of America, the Radiological Society of North America, and the Tissue Culture Society. He has served on various review groups for the National Institutes of Health and the Environmental Protection Agency and has represented the United States in formulating health safety guidelines with the Organisation for Economic Co-operation and Development. His current research interests include the interaction of environmental agents on human health and new methods in the treatment of human cancer.